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Typed or Printed Name	<u>Mathew OTS</u>	Express Mail No.	EL 563 650 743 US
Signature	<u>[Signature]</u>	Date	<u>11-13-00</u>

**UTILITY
PATENT APPLICATION
TRANSMITTAL**

(Only for new nonprovisional applications under 37 CFR 1.53(b))

Atty Docket No.	IRVN-007CON
First Named Inventor	Gatanaga, et al.
Title:	Factors Affecting Tumor Necrosis Factor Receptor Releasing Enzyme Activity

APPLICATION ELEMENTS

See MPEP chapter 600 concerning utility patent application contents

Address to: Assistant Commissioner for Patents
Box Patent Application
Washington, D.C. 20231

1. X Fee Transmittal Form
2. X Specification Total Pages 100
(preferred arrangement set forth below)
- Descriptive title of the invention
- Cross Reference to Related Applications
- Statement Regarding Fed sponsored R & D
- Reference to Microfiche Appendix

- Background of the Invention

- Brief Summary of the Invention
- Brief Description of the Drawings (if filed)
- Detailed Description
- Claim(s)
- Abstract of the Disclosure
3. X Drawing(s) (35 USC 113) Total Sheets 05
4. X Oath or Declaration Total Sheets 02

a. X Newly executed (original or copy)
b. Copy from a prior application (37 CFR 1.63(d)
(for continuation/divisional with Box 16 completed)

i. **DELETION OF INVENTOR(S)**
Signed statement attached deleting
inventor(s) named in the prior application,
see 37 CFR 1.63(d)(2) and 1.33(b)

c. Unsigned

5. Microfiche Computer Program (*Appendix*)
6. X Nucleotide and/or Amino Acid Sequence Submission
(*if applicable, all necessary*)

a. X Computer Readable Copy (from prior application)
b. X Paper Copy (identical to computer copy)
c. X Statement verifying identity of above copies

ACCOMPANYING APPLICATION PARTS

7. Assignment Papers (cover sheet & document(s))
8. 37 CFR 3.73(b) Statement Power of
(*when there is an assignee*) Attorney
9. English Translation Document (*if applicable*)
10. Information Disclosure
Statement (IDS)/PTO-1449 Copies of IDS
Citations
11. X Preliminary Amendment
12. Return Receipt Postcard (MPEP 503)
(*Should be specifically itemized*)
13. X Small Entity: The Undersigned hereby asserts that
Applicants are entitled to small entity
status.
14. Certified Copy of Priority Document(s)
(*if foreign priority is claimed*)
15. Other:

16. If a CONTINUING APPLICATION, check appropriate box and supply the requisite information:

X Continuation Divisional Continuation-in-part (CIP) of prior application No. 09/081,385, filed May 14, 1998 and
of Prior Application No. PCT/US99/10793, filed May 14, 1999.

UTILITY PATENT APPLICATION TRANSMITTAL
 (Only for new non-provisional applications under 37 CFR 1.53(b))

17. CORRESPONDENCE ADDRESS			
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Individual Name	Carol L. Francis
Registration No.	36,513
Signature	<i>Carol L. Francis</i>
Date	<i>November 13, 2000</i>

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FEE TRANSMITTAL

Note: Effective October 1, 1998.
Patent fees are subject to annual revision.

Attorney Docket Number	IRVN-007CON
First Named Inventor	Gatanaga, et al.
Application Number	N/A
Filing Date	Herewith
Group Art Unit	N/A
Examiner Name	N/A

METHOD OF PAYMENT

1. ☐ A Check Is Enclosed
 2. ☒ The Commissioner is hereby authorized to charge the following and any additional fees including fees required under 37 CFR 1.16 and 1.17 and credit any overpayments to: Deposit Account No. 50-0815.
 Deposit Account Name: Bozicevic, Field & Francis LLP

FEE CALCULATION

1. FILING FEE

Large Fee Code	Entity Fee (\$)	Small Fee Code	Entity Fee (\$)	Fee Description	Fee Due
101	710	201	355	Utility filing fee	\$355
102	320	206	160	Design filing fee	
104	490	207	245	Plant filing fee	
109	710	208	355	Reissue filing fee	
110	150	214	75	Provisional filing fee	
Subtotal (1)					\$355

2. CLAIMS

No. of claims as filed after amendment	Most claims previously paid	Extra claims	Fee from below	Fee Due
Total claims	11	20	x 00	\$
Ind. claims	02	03	x 00	
Multiple Dependent claims			x 135	\$135

Large Fee Code	Entity Fee (\$)	Small Fee Code	Entity Fee (\$)	Fee Description	Fee Due
103	18	203	9	Claims in excess of 20	
102	80	202	40	Independent claims in excess of 3	
104	270	204	135	Multiple dependent claim	
109	80	209	40	Reissue independent claims over original patent	
110	18	210	9	Reissue claims in excess of and over original patent	
Subtotal (2) \$135					

3. ADDITIONAL FEES


Large Fee Code	Entity Fee (\$)	Small Fee Code	Entity Fee (\$)	Fee Description	Fee Due
105	130	205	65	Surcharge - late filing fee or oath	
139	130	139	130	Non-English specification	
115	110	215	55	Ext. for reply within first month	
117	890	217	445	Ext. for reply within third month	
128	1,890	228	945	Ext. for reply within fifth month	
120	310	220	155	Filing brief in support of appeal	
140	110	240	55	Petition to revive - unavoidable	
142	1,240	242	620	Utility issue fee (or reissue)	
123	50	123	50	Petitions related to prov. appl.	
146	710	246	355	Filing submission after final rejection (37 CFR 1.129(a))	
112	920*	112	920*	Requesting publication of SIR prior to Examiner action	
143	440	243	220	Design issue fee	
581	40	581	40	Recording patent assignment	
* Reduced by Basic Filing Fee Paid					

SUBTOTAL (3) \$00.00

TOTAL AMOUNT TO BE CHARGED (\$) \$490.00

SUBMITTED BY

Typed or Printed Name	Complete (if applicable)
Carol L. Francis, BOZICEVIC, FIELD & FRANCIS LLP	Reg. Number 36,513
Signature <i>Carol L. Francis</i>	Deposit Account 50-0815
Date Nov 13, 2002	

EXPRESS MAIL CERTIFICATE			
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Typed or Printed Name	Mathew Otts	Express Mail No.	EL 563 650 743 US
Signature		Date	November 13, 2000
PRELIMINARY AMENDMENT Address to: Commissioner for Patents Washington, D.C. 20231	Attorney Docket	IRVN-007CON (UC 96-367-5)	
	First Named Inventor	Gatanaga, et al.	
	Application Number	N/A	
	Filing Date	Herewith	
	Group Art Unit	N/A	
	Examiner Name	N/A	
	Title	Factors Affecting Tumor Necrosis Factor Receptor Releasing Enzyme Activity	

Sir:

Prior to the examination on the merits of the above-referenced application, please amend the application as follows.

AMENDMENTS

In the Specification:

On page 1, line 5, after "pending", insert --and of International Application No. PCT/US99/10793, filed May 14, 1999--.

On page 1, line 6, delete "application is" and insert therefore --applications are--.

On page 1, line 6, delete "its" and insert therefore --their--.

In The Claims:

Cancel claims 1-36 without prejudice.

Add the following new claims:

-- 37. (New) An isolated polynucleotide comprising a nucleotide sequence expressed at the mRNA level in human mononuclear leukocytes having cell-surface TNF receptor, thereby increasing cleavage and release of the receptor from the surface of the cell.

38. (New) The isolated polynucleotide of claim 1, wherein the nucleotide sequence is expressed at the mRNA level in Jurkat T cells; and when COS-1 cells expressing TNF receptor are genetically altered to express the sequence, the cells have increased enzymatic activity for cleaving and releasing the receptor.

39. (New) The polynucleotide of claim 37 or 38, having one or more of the following properties:

- a) the polynucleotide comprises a nucleotide sequence contained in SEQ ID NOs:1-10;
 - b) the polynucleotide comprises a nucleotide sequence of at least 30 consecutive nucleotides contained in SEQ ID NOs:1-10;
 - c) the polynucleotide comprises a nucleotide sequence of at least 50 consecutive nucleotides at least 90% identical to a sequence contained in SEQ ID NOs:1-10; or
 - d) the polynucleotide is capable of hybridizing specifically to a nucleotide sequence contained in SEQ ID NOs:1-10 under stringent conditions; or
 - e) the polynucleotide comprises a nucleotide sequence that encodes at least 10 consecutive amino acids encoded in SEQ ID NOs:1-10;
- wherein the polynucleotide has at least one of the following properties:
- i) the polynucleotide encodes a polypeptide which, when incubated with COS-1 cells expressing TNF receptor, promotes enzymatic cleavage and release of the receptor; or
 - ii) the polynucleotide is a labeled probe or amplification primer that specifically identifies a polynucleotide comprising SEQ ID NOs:1-10.

40. (New) The polynucleotide of claim 39 that comprises a nucleotide sequence of at least 30 consecutive nucleotides contained in SEQ ID NOs:1-10.

41. (New) The polynucleotide of claim 39 that encodes a polypeptide which, when incubated with COS-1 cells expressing TNF receptor, promotes enzymatic cleavage and release of the receptor

42. (New) The polynucleotide of claim 39 that is a labeled probe or amplification *primer*.

43. (New) A host cell genetically altered with a polynucleotide according to claim 39.

44. (New) A method for increasing signal transduction from a cytokine into a cell, comprising contacting the cell with a polynucleotide having at least one of the following properties:

- i) the polynucleotide comprises a nucleotide sequence contained in SEQ ID NOs:1-10;
- ii) the polynucleotide comprises a nucleotide sequence of at least 30 consecutive nucleotides contained in SEQ ID NOs:1-10;
- iii) the polynucleotide comprises a nucleotide sequence of at least 50 consecutive nucleotides at least 90% identical to a sequence contained in SEQ ID NOs:1-10; or
- iv) the polynucleotide is capable of hybridizing specifically to a nucleotide sequence contained in SEQ ID NOs:1-10 under stringent conditions.

45. (New) The method of claim 44, wherein the polynucleotide comprises a nucleotide sequence of at least 30 consecutive nucleotides contained in SEQ ID NOs:1-10.

46. (New) The method of claim 44, wherein the cytokine is TNF.--

REMARKS

Claims 37-46 are pending after entry of the amendments above.

Claims 1-36 are canceled without prejudice to renewal, without intent to abandon any subject matter therein, and without acquiescing to any rejection which may have been applied. Applicants expressly reserve the right to pursue the subject matter of the canceled claims in a continuing application.

Support for new claims 37-38 is found in, for example, claim 1 as originally filed.

Support for new claims 39-40 is found in, for example, claims 2-5 and 9 as originally filed.

Support for new claim 41 is found in, for example, claim 11 as originally filed.

Support for new claims 42 is found in, for example, the specification at page 11, line 14 and page 17, lines 1-11.

Support for new claim 43 is found in, for example, the specification at page 14, lines 26-27.

Support for new claim 44 is found in, for example, claim 22 as originally filed.

Support for new claim 46 is found in, for example, claim 23 as originally filed.

No new matter is added.

CONCLUSION

Applicants respectfully submit that the claims are in form for allowance, early notice of which is requested. If, in the opinion of the Examiner a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned at (650) 327-3400.

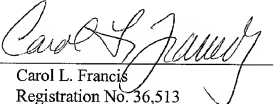
The Commissioner is hereby authorized to charge any fees under 37 C.F.R. §§ 1.16 and 1.17 which may be required by this paper, or to credit any overpayment, to Deposit Account No. 50-0815.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date:

November 13, 2022

By:


Carol L. Francis
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Date of Deposit: November 13, 2000

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Mathew OTTS

Typed or Printed Name of Person Mailing Paper or Fee

Mathew OTTS

Signature of Person Mailing Paper or Fee

PATENT APPLICATION

for

FACTORS AFFECTING TUMOR NECROSIS FACTOR RECEPTOR RELEASING ENZYME ACTIVITY



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**FACTORS AFFECTING TUMOR NECROSIS FACTOR RECEPTOR
RELEASING ENZYME ACTIVITY**

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the priority benefit of U.S. application 09/081,385,
5 filed May 14, 1998, pending. For purposes of prosecution in the U.S., the priority
application is hereby incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

10 This invention relates generally to the field of signal transduction between
cells, via cytokines and their receptors. More specifically, it relates to enzymatic
activity that cleaves and releases the receptor for TNF found on the cell surface,
and the consequent biological effects. Certain embodiments of this invention are
compositions that affect such enzymatic activity, and may be included in
medicaments for disease treatment.

BACKGROUND OF THE INVENTION

15 Cytokines play a central role in the communication between cells.
Secretion of a cytokine from one cell in response to a stimulus can trigger an
adjacent cell to undergo an appropriate biological response — such as
20 stimulation, differentiation, or apoptosis. It is hypothesized that important
biological events can be influenced not only by affecting cytokine release from
the first cell, but also by binding to receptors on the second cell, which mediates
the subsequent response. The invention described in this patent application
provides new compounds for affecting signal transduction from tumor necrosis
25 factor.

The cytokine known as tumor necrosis factor (TNF or TNF- α) is
structurally related to lymphotoxin (LT or TNF- β). They have about 40 percent
amino acid sequence homology (Old, *Nature* 330:602-603, 1987). These
cytokines are released by macrophages, monocytes and natural killer cells and

play a role in inflammatory and immunological events. The two cytokines cause a broad spectrum of effects both in vitro and in vivo, including: (i) vascular thrombosis and tumor necrosis; (ii) inflammation; (iii) activation of macrophages and neutrophils; (iv) leukocytosis; (v) apoptosis; and (vi) shock. TNF has been associated with a variety of disease states including various forms of cancer, arthritis, psoriasis, endotoxic shock, sepsis, autoimmune diseases, infections, obesity, and cachexia. TNF appears to play a role in the three factors contributing to body weight control: intake, expenditure, and storage of energy (Rothwell, *Int. J. Obesity* 17:S98-S101, 1993). In septicemia, increased endotoxin concentrations appear to raise TNF levels (Beutler et al. *Science* 229:869-871, 1985).

Attempts have been made to alter the course of a disease by treating the patient with TNF inhibitors, with varying degrees of success. For example, the TNF inhibitor dexamabolin provided protection against TNF mediated effects following traumatic brain injury (Shohami et al. *J. Neuroimmun.* 72:169-77, 1997). Some improvement in Crohn's disease was afforded by treatment with anti-TNF antibodies (Neurath et al., *Eur. J. Immun.* 27:1743-50, 1997).

Human TNF and LT mediate their biological activities by binding specifically to two distinct glycoprotein plasma membrane receptors (55 kDa and 75 kDa in size, known as p55 and p75 TNF-R, respectively). The two receptors share 28 percent amino acid sequence homology in their extracellular domains, which are composed of four repeating cysteine-rich regions (Tartaglia and Goeddel, *Immunol. Today* 13:151-153, 1992). However, the receptors lack significant sequence homology in their intracellular domains, and mediate different intracellular responses to receptor activation. In accordance with the different activities of TNF and LT, most human cells express low levels of both TNF receptors: about 2,000 to 10,000 receptors per cell (Brockhaus et al., *Proc. Natl. Acad. Sci. USA* 87:3127-3131, 1990).

Expression of TNF receptors on both lymphoid and non-lymphoid cells can be influenced experimentally by many different agents, such as bacterial lipopolysaccharide (LPS), phorbol myristate acetate (PMA; a protein kinase C

activator), interleukin-1 (IL-1), interferon-gamma (IFN- γ) and IL-2 (Gatanaga et al. *Cell Immunol.* 138:1-10, 1991; Yui et al. *Placenta* 15:819-835, 1994). It has been shown that complexes of human TNF bound to its receptor are internalized from the cell membrane, and then the receptor is either degraded or recycled (Armitage, *Curr. Opin. Immunol.* 6:407-413, 1994). It has been proposed that TNF receptor activity can be modulated using peptides that bind intracellularly to the receptor, or which bind to the ligand binding site, or that affect receptor shedding. See for example patent publications WO 95/31544, WO 95/33051, WO 96/01642, and EP 568 925.

10 TNF binding proteins (TNF-BP) have been identified at elevated levels in the serum and urine of febrile patients, patients with renal failure, and cancer patients, and even certain healthy individuals. Human brain and ovarian tumors produced high serum levels of TNF-BP. These molecules have been purified, characterized, and cloned (Gatanaga et al., *Lymphokine Res.* 9:225-229, 1990a; Gatanaga et al., *Proc. Natl. Acad. Sci USA* 87:8781-8784, 1990b). Human TNF-BP consists of 30 kDa and 40 kDa proteins which are identical to the N-terminal extracellular domains of p55 and p75 TNF receptors, respectively (US Patent No. 5,395,760; EP 418,014). Such proteins have been suggested for use in treating endotoxic shock. Mohler et al. *J. Immunol.* 151:1548-1561, 1993

20 There are several mechanisms possible for the production of secreted proteins resembling membrane bound receptors. One involves translation from alternatively spliced mRNAs lacking transmembrane and cytoplasmic regions. Another involves proteolytic cleavage of the intact membrane receptors, followed by shedding of the cleaved receptor from the cell. The soluble form of p55 and p75 TNF-R do not appear to be generated from mRNA splicing, since only full length receptor mRNA has been detected in human cells *in vitro* (Gatanaga et al., 1991). Carboxyl-terminal sequencing and mutation studies on human p55 TNF-R indicates that a cleavage site may exist between residues Asn 172 and Val 173 (Gullberg et al. *Eur. J. Cell. Biol.* 58:307-312, 1992).

30 There are reports that a specific metalloprotease inhibitor, TNF- α protease inhibitor (TAPI) blocks the shedding of soluble p75 and p55 TNF-R (Crowe et al.

5 J. Exp. Med. 181:1205-1210, 1995; Mullberg et al. J. Immunol. 155:5198-5205, 1995). The processing of pro-TNF on the cell membrane to release the TNF ligand appears to be dependent on a matrix metalloprotease like enzyme (Gearing et al. Nature 370:555-557, 1994). This is a family of structurally related matrix-degrading enzymes that play a major role in tissue remodeling and repair associated with development and inflammation (Birkedal-Hansen et al. Crit. Rev. Oral Biol. Med. 4:197-250, 1993). The enzymes have Zn^{2+} in their catalytic domains, and Ca^{2+} stabilizes their tertiary structure significantly.

10 In European patent application EP 657536A1, Wallach et al. suggest that it would be possible to obtain an enzyme that cleaves the 55,000 kDa TNF receptor by finding a mutated form of the receptor that is not cleaved by the enzyme, but still binds to it. The only proposed source for the enzyme is a detergent extract of membranes for cells that appear to have the protease activity. If it were possible to obtain an enzyme according to this scheme, then
15 the enzyme would presumably comprise a membrane spanning region. The patent application does not describe any protease that was actually obtained.

In a previous patent application in the present series (International Patent Publication WO 9820140), methods are described for obtaining an isolated enzyme that cleaves both the p55 and p75 TNF-R from cell surfaces. A
20 convenient source is the culture medium of cells that have been stimulated with phorbol myristate acetate (PMA). The enzyme activity was given the name TRRE (TNF receptor releasing enzyme). In other studies, TRRE was released immediately upon PMA stimulation, indicating that it is presynthesized in an inactive form to be rapidly converted to the active form upon stimulation.
25 Evidence for direct cleavage of TNF-R is that the shedding begins very quickly (~5 min) with maximal shedding within 30 min. TRRE is specific for the TNF-R, and does not cleave IL-1 receptors, CD30, ICAM-1 or CD11b. TRRE activity is enhanced by adding Ca^{++} or Zn^{++} , and inhibited by EDTA and phenantroline.

Given the involvement of TNF in a variety of pathological conditions, it is
30 desirable to obtain a variety of factors that would allow receptor shedding to be

modulated, thereby controlling the signal transduction from TNF at a disease site.

SUMMARY OF THE INVENTION

5 This disclosure provides new compounds that promote enzymatic cleavage and release of TNF receptors from the cell surface. Nine new DNA clones have been selected after repeat screening in an assay that tests the ability to enhance receptor release. The polynucleotide sequences of this invention and the proteins encoded by them have potential as diagnostic aids,
10 and therapeutic compounds that can be used to adjust TNF signal transduction in a beneficial way.

One embodiment of the invention is an isolated polynucleotide comprising a nucleotide sequence with the following properties: a) the sequence is expressed at the mRNA level in Jurkat T cells; b) when COS-1 cells expressing
15 TNF-receptor are genetically transformed to express the sequence, the cells have increased enzymatic activity for cleaving and releasing the receptor. If a polynucleotide sequence is expressed in Jurkat cells, then it can be found in the Jurkat cell expression library deposited with the ATCC (Accession No. TIB-152). It is recognized that the polynucleotide can be obtained from other cell lines, or
20 produced by recombinant techniques.

Included are polynucleotides in which the nucleotide sequence is contained in any of SEQ. ID NOS:1-10. Also embodied are polynucleotides comprising at least 30 and preferably more consecutive nucleotides in said nucleotide sequence, or at least 50 consecutive nucleotides that are homologous
25 to said sequence at a significant level, preferably at the 90% level or more. Also included antisense and ribozyme polynucleotides that inhibit the expression of a TRRE modulator.

Another embodiment of the invention is isolated polypeptides comprising an amino acid sequence encoded by a polynucleotide of this invention. Non-
30 limiting examples are sequences shown in SEQ. ID NOS: 147-158. Fragments

and fusion proteins are included in this invention, and preferably comprise at least 10 consecutive residues encoded by a polynucleotide of this invention, or at least 15 consecutive amino acids that are homologous at a significant level, preferably at least 80%. Preferred polypeptides promote cleavage and release of TNF receptors from the cell surface, especially COS-1 cells genetically transformed to express TNF receptor. The polypeptides may or may not have a membrane spanning domain, and may optionally be produced by a process that involves secretion from a cell. Included are species homologs with the desired activity, and artificial mutants with additional beneficial properties.

Another embodiment of this invention is an antibody specific for a polypeptide of this invention. Preferred are antibodies that bind a TRRE modulator protein, but not other substances found in human tissue samples in comparable amounts.

Another embodiment of the invention is an assay method of determining altered TRRE activity in a cell or tissue sample, using a polynucleotide or antibody of this invention to detect the presence or absence of the corresponding TRRE modulator. The assay method can optionally be used for the diagnosis or evaluation of a clinical condition relating to abnormal TNF levels or TNF signal transduction.

Another embodiment of the invention is a method for increasing or decreasing signal transduction from a cytokine into a cell (including but not limited to TNF), comprising contacting the cell with a polynucleotide, polypeptide, or antibody of this invention.

A further embodiment of the invention is a method for screening polynucleotides for an ability to modulate TRRE activity. The method involves providing cells that express both TRRE and the TNF-receptor; genetically altering the cells with the polynucleotides to be screened; cloning the cells; and identifying clones with the desired activity.

Yet another embodiment of the invention is a method for screening substances for an ability to affect TRRE activity. This typically involves incubating cells expressing TNF receptor with a TRRE modulator of this

invention in the presence or absence of the test substance; and measuring the effect on shedding of the TNF receptor .

The products of this invention can be used in the preparation of a medicament for treatment of the human or animal body. The medicament contains a clinically effective amount for treatment of a disease such as heart failure, cachexia, inflammation, endotoxic shock, arthritis, multiple sclerosis, sepsis, and cancer. These compositions can be used for administration to a subject suspected of having or being at risk for the disease, optionally in combination with other forms of treatment appropriate for their condition.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a schematic representation of plasmid pCDTR2. This plasmid expresses p75 TNF-R, the ~75 kDa form of the TNF receptor. PCMV stands for cytomegalovirus; BGHpA stands for bovine growth hormone polyadenylation signal.

Figure 2 is a line depicting the levels of p75 TNF-R detected on COS-1 cells genetically altered to express the receptor. Results from the transformed cells, designated C75R (●, upward swooping line) is compared with that from the parental COS-1 cells (■, baseline). The receptor number was calculated by Scatchard analysis (inset).

Figure 3 is a survival graph, showing that TRRE decreases mortality in mice challenged with lipopolysaccharide (LPS) to induce septic peritonitis. (♦) LPS alone; (■) LPS plus control buffer; (●) LPS plus TRRE (2,000 U); (▲) LPS plus TRRE (4,000 U).

Figure 4 is a half-tone reproduction of a bar graph, showing the effect of 9 new clones on TRRE activity on C75R cells (COS-1 cells transfected to express the TNF-receptor. Each of the 9 clones increases TRRE activity by over 2-fold.

Figure 5 is a survival graph, showing the ability of 4 new expressed to save mice challenged with LPS. (♦) saline; (■) BSA; (Δ) Mey-3 (100 μg); (X) Mey-3 (10 μg); (*) Mey-5 (10 μg); (●) Mey-8 (10 μg).

DETAILED DESCRIPTION OF THE INVENTION

It has been discovered that certain cells involved in the TNF transduction pathway express enzymatic activity that causes TNF receptors to be shed from the cell surface. Enzymatic activity for cleaving and releasing TNF receptors has
5 been given the designation TRRE. Phorbol myristate acetate induces release of TRRE from cells into the culture medium. An exemplary TRRE protein had been purified from the supernatant of TNF-1 cells (Example 2). The protease bears certain hallmarks of the metalloprotease family, and is released rapidly from the
10 cell upon activation.

In order to elucidate the nature of this protein, functional cloning was performed. Jurkat cells were selected as being a good source of TRRE. The cDNA from a Jurkat library was expressed, and cell supernatant was tested for an ability to release TNF receptors from cell surfaces. Cloning and testing of the
15 expression product was conducted through several cycles, and nine clones were obtained that more than doubled TRRE activity in the assay (Figure 4). At the DNA level, all 9 clones had different sequences.

Protein expression products from the clones have been tested in a lipopolysaccharide animal model for sepsis. Protein from three different clones
20 successfully rescued animals from a lethal dose of LPS (Figure 5). This points to an important role for these molecules in the management of pathological conditions mediated by TNF.

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The number of new TRRE promoting clones obtained from the expression library was surprising. The substrate specificity of the TRRE isolated in Example 2 distinguishes the 75 kDa and 55 kDa TNF receptors from other cytokine receptors and cell surface proteins. There was little reason beforehand to suspect that cells might have nine different proteases for the TNF receptor. It is possible that one of the clones encodes the TRRE isolated in Example 2, or a related protein. It is possible that some of the other clones have proteolytic activity to cleave TNF receptors at the same site, or at another site that causes release of the soluble form from the cell. It is a hypothesis of this disclosure that some of the clones may not have proteolytic activity themselves, but play a role in promoting TRRE activity in a secondary fashion.

This possibility is consistent with the observations made, because there is an endogenous level of TRRE activity in the cells used in the assay. The cleavage assay involves monitoring TNF receptor release from C75 cells, which are COS-1 cells genetically altered to express p75 TNF-R. The standard assay is conducted by contacting the transformed cells with a fluid believed to contain TRRE. The level of endogenous TRRE activity is evident from the rate of spontaneous release of the receptor even when no exogenous TRRE is added (about 200 units). Accordingly, accessory proteins that promote TRRE activity would increase the activity measured in the assay. Many mechanisms of promotion are possible, including proteins that activate a zymogen form of TRRE, proteins that free TRRE from other cell surface components, or proteins that stimulate secretion of TRRE from inside the cell. It is not necessary to understand the mechanism in order to use the products of this invention in most of the embodiments described.

It is anticipated that several of the clones will have activity not just for promoting TNF receptor cleavage, but also having an effect on other surface proteins. To the extent that cleavage sequences or accessory proteins are shared between different receptors, certain clones would promote phenotypic change (such as receptor release) for the family of related substrates.

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This disclosure provides polypeptides that promote TRRE activity, polynucleotides that encode such polypeptides, and antibodies that bind such peptides. The binding of TNF to its receptor mediates a number of biological effects. Cleavage of the TNF-receptor by TRRE diminishes signal transduction by TRRE. Potentiators of TRRE activity have the same effect. Thus, the products of this invention can be used to modulate signal transduction by cytokines, which is of considerable importance in the management of disease conditions that are affected by cytokine action. The products of this invention can also be used in diagnostic methods, to determine when signal transduction is being inappropriately affected by abnormal TRRE activity. The assay systems described in this disclosure provide a method for screening additional compounds that can influence TRRE activity, and thus the signal transduction from TNF.

Based on the summary of the invention, and guided by the illustrations in the example section, one skilled in the art will readily know what techniques to employ in the practice of the invention. The following detailed description is provided for the additional convenience of the reader.

Definitions and basic techniques

As used in this disclosure, "TRRE activity" refers to the ability of a composition to cleave and release TNF receptors from the surface of cells expressing them. A preferred assay is cleavage from transfected COS-1 cells, as described in Example 1. However, TRRE activity can be measured on any cells that bear TNF receptors of the 55 kDa or 75 kDa size. Other features of the TRRE enzyme obtained from PMA induction of THP-1 cells (exemplified in Example 2) need not be a property of the TRRE activity measured in the assay.

Unit activity of TRRE is defined as 1 pg of soluble p75 TNF-R released from cell surface in a standard assay, after correction for spontaneous release. The measurement of TRRE activity is explained further in Example 1.

A "TRRE modulator" is a compound that has the property of either increasing or decreasing TRRE activity for processing TNF on the surface of

cells. Those that increase TRRE activity may be referred to as TRRE promoters, and those that decrease TRRE activity may be referred to as TRRE inhibitors. TRRE promoters include compounds that have proteolytic activity for TNF-R, and compounds that augment the activity of TNF-R proteases. The nine polynucleotide clones described in Example 5, and their protein products, are exemplary TRRE promoters. Inhibitors of TRRE activity can be obtained using the screening assays described below.

The term "polynucleotide" refers to a polymeric form of nucleotides of any length, either deoxyribonucleotides or ribonucleotides, or analogs thereof. Polynucleotides may have any three-dimensional structure, and may perform any function, known or unknown. The following are non-limiting examples of polynucleotides: a gene or gene fragment, exons, introns, (mRNA), ribozymes, cDNA, recombinant polynucleotides, branched polynucleotides, plasmids, vectors, nucleic acid probes, and primers. A polynucleotide may comprise modified nucleotides, such as methylated nucleotides and nucleotide analogs. If present, modifications to the nucleotide structure may be imparted before or after assembly of the polymer. The term polynucleotide refers interchangeably to double- and single-stranded molecules. Unless otherwise specified or required, any embodiment of the invention described herein that is a polynucleotide encompasses both the double-stranded form, and each of two complementary single-stranded forms known or predicted to make up the double-stranded form

"Hybridization" refers to a reaction in which one or more polynucleotides react to form a complex that is stabilized via hydrogen bonding between the bases of the nucleotide residues. Hybridization reactions can be performed under conditions of different "stringency". Relevant conditions include temperature, ionic strength, and the presence of additional solutes in the reaction mixture such as formamide. Conditions of increasing stringency are 30°C. in 10X SSC (0.15M NaCl, 15 mM citrate buffer); 40°C. in 6X SSC; 50°C. in 6X SSC; 60°C. in 6X SSC, or at about 40°C. in 0.5X SSC, or at about 30°C. in 6X SSC containing 50% formamide. SDS and a source of fragmented DNA (such as salmon sperm) are typically also present during hybridization. Higher

stringency requires higher minimum complementarity between hybridizing elements for a stable hybridization complex to form. See "Molecular Cloning: A Laboratory Manual", Second Edition (Sambrook, Fritsch & Maniatis, 1989).

5 It is understood that purine and pyrimidine nitrogenous bases with similar structures can be functionally equivalent in terms of Watson-Crick base-pairing; and the inter-substitution of like nitrogenous bases, particularly uracil and thymine, or the modification of nitrogenous bases, such as by methylation, does not constitute a material substitution.

10 The percentage of sequence identity for polynucleotides or polypeptides is calculated by aligning the sequences being compared, and then counting the number of shared residues at each aligned position. No penalty is imposed for the presence of insertions or deletions, but are permitted only where required to accommodate an obviously increased number of amino acid residues in one of the sequences being aligned. When one of the sequences being compared is
15 indicated as being "consecutive", then no gaps are permitted in that sequence during the comparison. The percentage identity is given in terms of residues in the test sequence that are identical to residues in the comparison or reference sequence.

20 As used herein, "expression" of a polynucleotide refers to the production of an RNA transcript. Subsequent translation into protein or other effector compounds may also occur, but is not required unless specified.

"Genetic alteration" refers to a process wherein a genetic element is introduced into a cell other than by mitosis or meiosis. The element may be heterologous to the cell, or it may be an additional copy or improved version of
25 an element already present in the cell. Genetic alteration may be effected, for example, by transducing a cell with a recombinant plasmid or other polynucleotide through any process known in the art, such as electroporation, calcium phosphate precipitation, or contacting with a polynucleotide-liposome complex. Genetic alteration may also be effected, for example, by transduction
30 or infection with a DNA or RNA virus or viral vector. It is preferable that the

genetic alteration is inheritable by progeny of the cell, but this is not generally required unless specified.

The terms "polypeptide", "peptide" and "protein" are used interchangeably herein to refer to polymers of amino acids of any length. The polymer may be linear or branched, it may comprise modified amino acids, and it may be interrupted by non-amino acids. The terms also encompass an amino acid polymer that has been modified; for example, disulfide bond formation, glycosylation, lipidation, acetylation, phosphorylation, or any other manipulation, such as conjugation with a labeling component.

A "fusion polypeptide" is a polypeptide comprising regions in a different position in the sequence than occurs in nature. The regions can normally exist in separate proteins and are brought together in the fusion polypeptide; they can normally exist in the same protein but are placed in a new arrangement in the fusion polypeptide; or they can be synthetically arranged. A "functionally equivalent fragment" of a polypeptide varies from the native sequence by addition, deletion, or substitution of amino acid residues, or any combination thereof, while preserving a functional property of the fragment relevant to the context in which it is being used. Fusion peptides and functionally equivalent fragments are included in the definition of polypeptides used in this disclosure.

It is understood that the folding and the biological function of proteins can accommodate insertions, deletions, and substitutions in the amino acid sequence. Some amino acid substitutions are more easily tolerated. For example, substitution of an amino acid with hydrophobic side chains, aromatic side chains, polar side chains, side chains with a positive or negative charge, or side chains comprising two or fewer carbon atoms, by another amino acid with a side chain of like properties can occur without disturbing the essential identity of the two sequences. Methods for determining homologous regions and scoring the degree of homology are described in Altschul et al. *Bull. Math. Bio.* 48:603-616, 1986; and Henikoff et al. *Proc. Natl. Acad. Sci. USA* 89:10915-10919, 1992. Substitutions that preserve the functionality of the polypeptide, or confer a new

and beneficial property (such as enhanced activity, stability, or decreased immunogenicity) are especially preferred.

5 An "antibody" (interchangeably used in plural form) is an immunoglobulin molecule capable of specific binding to a target, such as a polypeptide, through at least one antigen recognition site, located in the variable region of the immunoglobulin molecule. As used herein, the term encompasses not only intact antibodies, but also antibody equivalents that include at least one antigen combining site of the desired specificity. These include but are not limited to enzymatic or recombinantly produced fragments antibody, fusion proteins, 10 humanized antibodies, single chain variable regions, diabodies, and antibody chains that undergo antigen-induced assembly.

20 An "isolated" polynucleotide, polypeptide, protein, antibody, or other substance refers to a preparation of the substance devoid of at least some of the other components that may also be present where the substance or a similar substance naturally occurs or is initially obtained from. Thus, for example, an isolated substance may be prepared by using a purification technique to enrich it from a source mixture. Enrichment can be measured on an absolute basis, such as weight per volume of solution, or it can be measured in relation to a second, potentially interfering substance present in the source mixture. Increasing 25 enrichments of the embodiments of this invention are increasingly more preferred. Thus, for example, a 2-fold enrichment is preferred, 10-fold enrichment is more preferred, 100-fold enrichment is more preferred, 1000-fold enrichment is even more preferred. A substance can also be provided in an isolated state by a process of artificial assembly, such as by chemical synthesis or recombinant expression.

A "host cell" is a cell which has been genetically altered, or is capable of being transformed, by administration of an exogenous polynucleotide.

30 The term "clinical sample" encompasses a variety of sample types obtained from a subject and useful in an in vitro procedure, such as a diagnostic test. The definition encompasses solid tissue samples obtained as a surgical removal, a pathology specimen, or a biopsy specimen, cells obtained from a

clinical subject or their progeny obtained from culture, liquid samples such as blood, serum, plasma, spinal fluid, and urine, and any fractions or extracts of such samples that contain a potential indication of the disease.

Unless otherwise indicated, the practice of the invention will employ
5 conventional techniques of molecular biology, microbiology, recombinant DNA, and immunology, within the skill of the art. Such techniques are explained in the standard literature, such as: "Molecular Cloning: A Laboratory Manual", Second Edition (Sambrook, Fritsch & Maniatis, 1989), "Oligonucleotide Synthesis" (M. J. Gait, ed., 1984), "Animal Cell Culture" (R. I. Freshney, ed., 1987); the series
10 "Methods in Enzymology" (Academic Press, Inc.); "Handbook of Experimental Immunology" (D. M. Weir & C. C. Blackwell, Eds.), "Gene Transfer Vectors for Mammalian Cells" (J. M. Miller & M. P. Calos, eds., 1987), "Current Protocols in Molecular Biology" (F. M. Ausubel et al., eds., 1987); and "Current Protocols in Immunology" (J. E. Coligan et al., eds., 1991). The reader may also choose to
15 refer to a previous patent application relating to TRRE, International Patent Application WO 98020140.

For purposes of prosecution in the U.S., and in other jurisdictions where allowed, all patents, patent applications, articles and publications indicated
anywhere in this disclosure are hereby incorporated herein by reference in their
20 entirety.

Polynucleotides

Polynucleotides of this invention can be prepared by any suitable technique in the art. Using the data provided in this disclosure, sequences of
25 less than ~50 base pairs are conveniently prepared by chemical synthesis, either through a commercial service or by a known synthetic method, such as the triester method or the phosphite method. A preferred method is solid phase synthesis using mononucleoside phosphoramidite coupling units (Hirose et al., *Tetra. Lett.* 19:2449-2452, 1978; U.S. Patent No. 4,415,732).

30 For use in antisense therapy, polynucleotides can be prepared by chemistry that produce more stable in pharmaceutical preparations. Non-limiting

examples include thiol-derivatized nucleosides (U.S. Patent 5,578,718), and oligonucleotides with modified backbones (U.S. Patent Nos. 5,541,307 and 5,378,825).

Polynucleotides of this invention can also be obtained by PCR
5 amplification of a template with the desired sequence. Oligonucleotide primers spanning the desired sequence are annealed to the template, elongated by a DNA polymerase, and then melted at higher temperature so that the template and elongated oligonucleotides dissociate. The cycle is repeated until the
10 desired amount of amplified polynucleotide is obtained (U.S. Patent Nos. 4,683,195 and 4,683,202). Suitable templates include the Jurkat T cell library and other human or animal expression libraries that contain TRRE modulator encoding sequences. The Jurkat T cell library is available from the American Type Culture Collection, 10801 University Blvd., Manassas VA 20110, U.S.A. (ATCC #TIB-152). Mutations and other adaptations can be performed during
15 amplification by designing suitable primers, or can be incorporated afterwards by genetic splicing.

Production scale amounts of large polynucleotides are most conveniently obtained by inserting the desired sequence into a suitable cloning vector and reproducing the clone. Techniques for nucleotide cloning are given in Sambrook,
20 Fritsch & Maniatis (supra) and in U.S. Patent No. 5,552,524. Exemplary cloning and expression methods are illustrated in Example 6.

Preferred polynucleotide sequences are 50%, 70%, 80% , 90%, or 100% identical to one of the sequences exemplified in this disclosure; in order if increasing preference. The length of consecutive residues in the identical or
25 homologous sequence compared with the exemplary sequence can be about 15, 30, 50, 75, 100, 200 or 500 residues in order of increasing preference, up to the length of the entire clone. Nucleotide changes that cause a conservative substitution or retain the function of the encoded polypeptide (in terms of hybridization properties or what is encoded) are especially preferred
30 substitutions.

The polynucleotides of this can be used to measure altered TRRE activity in a cell or tissue sample. This involves contacting the sample with the polynucleotide under conditions that permit the polynucleotide to hybridize specifically with nucleic acid that encodes a modulator of TRRE activity, if present in the sample, and determining polynucleotide that has hybridized as a result of step a). Specificity of the test can be provided in one of several ways. One method involves the use of a specific probe — a polynucleotide of this invention with a sequence long enough and of sufficient identity to the sequence being detected, so that it binds the target and not other nucleic acid that might be present in the sample. The probe is typically labeled (either directly or through a secondary reagent) so that it can be subsequently detected. Suitable labels include ^{32}P and ^{33}P , chemiluminescent and fluorescent reagents. After the hybridization reaction, unreacted probe is washed away so that the amount of hybridized probe can be determined. Signal can be amplified using branched probes (U.S. Patent No. 5,124,246). In another method, the polynucleotide is a primer for a PCR reaction. Specificity is provided by the ability of the paired probes to amplify the sequence of interest. After a suitable number of PCR cycles, the amount of amplification product present correlates with the amount of target sequence originally present in the sample.

Such tests are useful both in research, and in the diagnosis or assessment of a disease condition. For example, TNF activity plays a role in eliminating tumor cells (Example 4), and a cancer may evade the elimination process by activating TRRE activity in the diseased tissue. Hence, under some conditions, high expression of TRRE modulators may correlate with progression of cancer. Diagnostic tests are also of use in monitoring therapy, such as when gene therapy is performed to increase TRRE activity.

Polynucleotides of this invention can also be used for production of polypeptides and the preparation of medicaments, as explained below.

Polypeptides

Short polypeptides of this invention can be prepared by solid-phase chemical synthesis. The principles of solid phase chemical synthesis can be found in Dugas & Penney, Bioorganic Chemistry, Springer-Verlag NY pp 54-92 (1981), and U.S. Patent No. 4,493,795. Automated solid-phase peptide synthesis can be performed using devices such as a PE-Applied Biosystems 430A peptide synthesizer (commercially available from Applied Biosystems, Foster City CA).

Longer polypeptides are conveniently obtained by expression cloning. A polynucleotide encoding the desired polypeptide is operably linked to control elements for transcription and translation, and then transfected into a suitable host cell. Expression may be effected in procaryotes such as E. coli (ATCC Accession No. 31446 or 27325), eukaryotic microorganisms such as the yeast *Saccharomyces cerevisiae*, or higher eukaryotes, such as insect or mammalian cells. A number of expression systems are described in U.S. Patent No. 5,552,524. Expression cloning is available from such commercial services as Lark Technologies, Houston TX. The production of protein from 4 exemplary clones of this invention in insect cells is illustrated in Example 6. The protein is purified from the producing host cell by standard methods in protein chemistry, such as affinity chromatography and HPLC. Expression products are optionally produced with a sequence tag to facilitate affinity purification, which can subsequently be removed.

Preferred sequences are 40%, 60%, 80%, 90%, or 100% identical to one of the sequences exemplified in this disclosure; in order of increasing preference. The length of the identical or homologous sequence compared with the native human polynucleotide can be about 7, 10, 15, 20, 30, 50 or 100 residues in order of increasing preference, up to the length of the entire encoding region.

Polypeptides can be tested for an ability to modulate TRRE in a TNF-R cleavage assay. The polypeptide is contacted with the receptor (preferably expressed on the surface of a cell, such as a C75 cell), and the ability of the polypeptide to increase or decrease receptor cleavage and release is

determined. Cleavage of TNF-R by exemplary polypeptides of this invention is illustrated in Example 7.

Polypeptides of this invention can be used as immunogens for raising antibody. Large proteins will raise a cocktail of antibodies, while short peptide fragments will raise antibodies against small region of the intact protein. Antibody clones can be mapped for protein binding site by producing short overlapping peptides of about 10 amino acids in length. Overlapping peptides can be prepared on a nylon membrane support by standard F-Moc chemistry, using a SPOTS™ kit from Genosys according to manufacturer's directions.

Polypeptides of this invention can also be used to affect TNF signal transduction, as explained below.

Antibodies

Polyclonal antibodies can be prepared by injecting a vertebrate with a polypeptide of this invention in an immunogenic form. Immunogenicity of a polypeptide can be enhanced by linking to a carrier such as KLH, or combining with an adjuvant, such as Freund's adjuvant. Typically, a priming injection is followed by a booster injection is after about 4 weeks, and antiserum is harvested a week later. Unwanted activity cross-reacting with other antigens, if present, can be removed, for example, by running the preparation over adsorbants made of those antigens attached to a solid phase, and collecting the unbound fraction. If desired, the specific antibody activity can be further purified by a combination of techniques, which may include protein, A chromatography, ammonium sulfate precipitation, ion exchange chromatography, HPLC, and immunoaffinity chromatography using the immunizing polypeptide coupled to a solid support. Antibody fragments and other derivatives can be prepared by standard immunochemical methods, such as subjecting the antibody to cleavage with enzymes such as papain or pepsin.

Production of monoclonal antibodies is described in such standard references as Harrow & Lane (1988), U.S. Patent Nos. 4,491,632, 4,472,500 and 4,444,887, and *Methods in Enzymology* 73B:3 (1981). Briefly, a mammal is

immunized, and antibody-producing cells (usually splenocytes) are harvested. Cells are immortalized by fusion with a non-producing myeloma, transfecting with Epstein Barr Virus, or transforming with oncogenic DNA. The treated cells are cloned and cultured, and the clones are selected that produce antibody of the
5 desired specificity.

Other methods of obtaining specific antibody molecules (optimally in the form of single-chain variable regions) involve contacting a library of immunocompetent cells or viral particles with the target antigen, and growing out positively selected clones. Immunocompetent phage can be constructed to
10 express immunoglobulin variable region segments on their surface. See Marks et al., *New Eng. J. Med.* 335:730, 1996, International Patent Applications WO 9413804, WO 9201047, WO 90 02809, and McGuinness et al., *Nature Biotechnol.* 14:1449, 1996.

The antibodies of this invention are can be used in immunoassays for
15 TRRE modulators. General techniques of immunoassay can be found in "The Immunoassay Handbook", Stockton Press NY, 1994; and "Methods of Immunological Analysis", Weinheim: VCH Verlags gesellschaft mbH, 1993). The antibody is combined with a test sample under conditions where the antibody will bind specifically to any modulator that might be present, but not any other
20 proteins liable to be in the sample. The complex formed can be measured in situ (U.S. Patent Nos. 4,208,479 and 4,708,929), or by physically separating it from unreacted reagents (U.S. Patent No. 3,646,346). Separation assays typically involve labeled TRRE reagent (competition assay), or labeled antibody (sandwich assay) to facilitate detection and quantitation of the complex. Suitable
25 labels are radioisotopes such as ¹²⁵I, enzymes such as β -galactosidase, and fluorescent labels such as fluorescein. Antibodies of this invention can also be used to detect TRRE modulators in fixed tissue sections by immunohistology. The antibody is contacted with the tissue, unreacted antibody is washed away, and then bound antibody is detected — typically using a labeled anti-
30 immunoglobulin reagent. Immunohistology will show not only whether the modulator is present, but where it is located in the tissue.

Detection of TRRE modulators is of interest for research purposes, and for clinical use. As indicated earlier, high expression of TRRE modulators may correlate with progression of cancer. Diagnostic tests are also of use in monitoring TRRE modulators that are administered in the course of therapy.

Antibodies of this invention can also be used for preparation of medicaments. Antibodies with therapeutic potential include those that affect TRRE activity — either by promoting clearance of a TRRE modulator, or by blocking its physiological action. Antibodies can be screened for desirable activity according to assays described in the next section.

Screening assays

This invention provides a number of screening methods for selecting and developing products that modulate TRRE, and thus affect TNF signal transduction.

One screening method is for polynucleotides that have an ability to modulate TRRE activity. To do this screening, cells are obtained that express both TRRE and the TNF receptor. Suitable cell lines can be constructed from any cell that expresses a level of functional TRRE activity. These cells are identifiable by testing culture supernatant for an ability to release membrane-bound TNF-R. The level of TRRE expression should be moderate, so that an increase in activity can be detected. The cells can then be genetically altered to express either p55 or p75 TNF-R, illustrated in Example 1. Exemplary is the C75R line: COS-1 cells genetically altered to express the 75 kDa form of the TNF-R. Release of TNF-R from the cell can be measured either by testing residual binding of labeled TNF ligand to the cell, or by immunoassay of the supernatant for released receptor (Example 1).

The screening assay is conducted by contacting the cells expressing TRRE and TNF-R with the polynucleotides to be screened. The effect of the polynucleotide on the enzymatic release of TNF-R from the cell is determined, and polynucleotides with desirable activity (either promoting or inhibiting TRRE activity) are selected. In a variation of this method, cells expressing TRRE

activity but not TNF-R (such as untransfected COS-1 cells) are contacted with the test polynucleotide. Then the culture medium is collected, and used to assay for TRRE activity using a second cell expressing TNF-R (such as C75 cells).

This type of screening assay is useful for the selection of polynucleotides from an expression library believed to contain encoding sequences for TRRE modulators. The Jurkat cell expression library (ATCC Accession No. TIB-152) is exemplary. Other cells from which suitable libraries can be constructed are those known to express high levels of TRRE, especially after PMA stimulation, such as THP-1, U-937, HL-60, ME-180, MRC-5, Raji, K-562, and normal human monocytes. The screening involves expressing DNA from the library in the selected cell line being used for screening. Wells with the desired activity are selected, and the DNA is recovered, optionally after replication or cloning of the cells. Repeat cycles of functional screening and selection can lead to identification of new polynucleotide clones that promote or inhibit TRRE activity. This is illustrated below in Example 5. Further experiments can be performed on the selected polynucleotides to determine if it modulates TRRE activity inside the cell, or through the action of a protein product. A long open reading frame suggests a role for a protein product, and examination of the amino acid sequence for a signal peptide and a membrane spanning region can help determine whether the protein is secreted from the cell or expressed in the surface membrane.

This type of screening is also useful for further development of the polynucleotides of this invention. For example, expression constructs can be developed that encode functional peptide fragments, fusion proteins, and other variants. The minimum size of polynucleotide sequence that still encodes TRRE modulation activity can be determined by removing part of the sequence and then using the screening assay to determine whether the activity is still present. Mutated and extended sequences can be tested in the same way.

This type of screening assay is also useful for developing compounds that affect TRRE activity by interfering with mRNA that encode a TRRE modulator. Of particular interest are ribozymes and antisense oligonucleotides. Ribozymes

are endoribonucleases that catalyze cleavage of RNA at a specific site. They comprise a polynucleotide sequence that is complementary to the cleavage site on the target, and additional sequence that provide the tertiary structure to effect the cleavage. Construction of ribozymes is described in U.S. Patent Nos. 5,498,071 and 5,591,610. Antisense oligonucleotides that bind mRNA comprise a short sequence complementary to the mRNA (typically 8-25 bases in length). Preferred chemistry for constructing antisense oligonucleotides is outlined in an earlier section. Specificity is provided both by the complementary sequence, and by features of the chemical structure. Antisense molecules that inhibit expression of cell surface receptors are described in U.S. Patent Nos. 5,135,917 and 5,789,573. Screening involves contacting the cell expressing TRRE activity and TNF-R with the compound and determining the effect on receptor release. Ribozymes and antisense molecules effective in altering expression of a TRRE promoter would decrease TNF-R release. Ribozymes and antisense molecules effective in altering expression of a TRRE inhibitor would increase TNF-R release.

Another screening method described in this disclosure is for testing the ability of polypeptides to modulate TRRE activity (Example 7). Cells expressing both TNF-R and a moderate level of TRRE activity are contacted with the test polypeptides, and the rate of receptor release is compared with the rate of spontaneous release. An increased rate of release indicates that the polypeptide is a TRRE promoter, while a decreased rate indicates that the polypeptide is a TRRE inhibitor. This assay can be used to test the activity of new polypeptides, and develop variants of polypeptides already known to modulate TRRE. The minimum size of polypeptide sequence that still encodes TRRE modulation activity can be determined by making a smaller fragment of the polypeptide and then using the screening assay to determine whether the activity is still present. Mutated and extended sequences can be tested in the same way.

Another screening method embodied in this invention is a method for screening substances that interfere with the action of a TRRE modulator at the protein level. The method involves incubating cells expressing TNF receptor

(such as C75R cells) with a polypeptide of this invention having TNF promoting activity. There are two options for supplying the TRRE modulator in this assay. In one option, the polypeptide is added to the medium of the cells as a reagent, along with the substance to be tested. In another option, the cells are genetically
5 altered to express the TRRE modulator at a high level, and the assay requires only that the test substance be contacted with the cells. This option allows for high throughput screening of a number of test compounds.

Either way, the rate of receptor release is compared in the presence and absence of the test substance, to identify compounds that enhance or diminish
10 TRRE activity. Parallel experiments should be conducted in which the activity of the substance on receptor shedding is tested in the absence of added polypeptide (using cells that don't express the polypeptide). This will determine whether the activity of the test substance occurs via an effect on the TRRE promoter being added, or through some other mechanism.

15 This type of screening assay is useful for identifying antibodies that affect the activity of a TRRE modulator. Antibodies are raised against a TRRE modulator as described in the previous section. If the antibody decreases TRRE activity in the screening assay, then it has therapeutic potential to lower TRRE activity in vivo. Screening of monoclonal antibodies using this assay can also
20 help identify binding or catalytic sites in the polypeptide.

This type of screening assay is also useful for high throughput screening of small molecule compounds that have the ability to affect the level of TNF receptors on a cell, by way of its influence on a TRRE modulator. Small molecule compounds that have the desired activity are often preferred for
25 pharmaceutical compositions, because they are often more stable and less expensive to produce.

Medicaments and their use

As described earlier, a utility of certain products embodied in this invention
30 is to affect signal transduction from cytokines (particularly TNF). Products that promote TRRE activity have the effect of decreasing TNF receptors on the

surface of cells, which would decrease signal transduction from TNF. Conversely, products that inhibit TRRE activity prevent cleavage of TNF receptors, increasing signal transduction.

The ability to affect TNF signal transduction is of considerable interest in the management of clinical conditions in which TNF signaling contributes to the pathology of the condition. Such conditions include:

- Heart failure. IL-1 β and TNF are believed to be central mediators for perpetuating the inflammatory process, recruiting and activating inflammatory cells. The inflammation depress cardiac function in congestive heart failure, transplant rejection, myocarditis, sepsis, and burn shock.
- Cachexia. The general weight loss and wasting occurring in the course of chronic diseases, such as cancer. TNF is believed to affect appetite, energy expenditure, and metabolic rate.
- Crohn's disease. The inflammatory process mediated by TNF leads to thickening of the intestinal wall, ensuing from lymphedema and lymphocytic infiltration.
- Endotoxic shock. The shock induced by release of endotoxins from gram-negative bacteria, such as *E. coli*, involves TNF-mediated inflammation.
- Arthritis. TNF promotes expression of nitric oxide synthetase, believed to be involved in disease pathogenesis.

Other conditions of interest are multiple sclerosis, sepsis, inflammation brought on by microbe infection, and diseases that have an autoimmune etiology, such as Type I Diabetes.

Polypeptides of this invention that promote TRRE activity can be administered with the objective of decreasing or normalizing TNF signal transduction. For example, in congestive heart failure or Crohn's disease, the polypeptide is given at regular intervals to lessen the inflammatory sequelae.

The treatment is optionally in combination with other agents that affect TNF

signal transduction (such as antibodies to TNF or receptor antagonists) or that lessen the extent of inflammation in other ways.

Polynucleotides of this invention can also be used to promote TRRE activity by gene therapy. The encoding sequence is operably linked to control elements for transcription and translation in human cells. It is then provided in a form that will promote entry and expression of the encoding sequence in cells at the disease site. Forms suitable for local injection include naked DNA, polynucleotides packaged with cationic lipids, and polynucleotides in the form of viral vectors (such as adenovirus and AAV constructs). Methods of gene therapy known to the practitioner skilled in the art will include those outlined in U.S. Patent Nos. 5,399,346, 5,827,703, and 5,866,696.

The ability to affect TNF signal transduction is also of interest where TNF is thought to play a beneficial role in resolving the disease. In particular, TNF plays a beneficial role in the necrotizing of solid tumors. Accordingly, products of this invention can be administered to cancer patients to inhibit TRRE activity, thereby increasing TNF signal transduction and improve the beneficial effect.

Embodiments of the invention that inhibit TRRE activity include antisense polynucleotides. A method of conferring long-standing inhibitory activity is to administer antisense gene therapy. A genetic construct is designed that will express RNA inside the cell which in turn will decrease the transcription of the target gene (U.S. Patent No. 5,759,829). In humans, a more frequent form of antisense therapy is to administer the effector antisense molecule directly, in the form of a short stable polynucleotide fragment that is complementary to a segment of the target mRNA (U.S. Patent Nos. 5,135,917 and 5,789,573) — in this case, the transcript that encodes the TRRE modulator. Another embodiment of the invention that inhibits TRRE are ribozymes, constructed as described in an earlier section. The function of ribozymes in inhibiting mRNA translation is described in U.S. Patent Nos. 4,987,071 and 5,591,610.

Once a product of this invention is found to have suitable TRRE modulation activity in the in vitro assays described in this disclosure, it is preferable to also test its effectiveness in an animal model of a TNF mediated

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disease process. Example 3 describes an LPS model for sepsis that can be used to test promoters of TRRE activity. Example 4 describes a tumor necrosis model, in which TRRE inhibitors could be tested for an ability to enhance necrotizing activity. Those skilled in the art will know of other animal models suitable for testing effects on TNF signal transduction or inflammation. Other illustrations are the cardiac ischemia reperfusion models of Weyrich et al. (*J. Clin. Invest.* 91:2620, 1993) and Garcia-Criado et al. (*J. Am. Coll. Surg.* 181:327, 1995); the pulmonary ischemia reperfusion model of Steinberg et al. (*J. Heart Lung Transplant.* 13:306, 1994), the lung inflammation model of International Patent Application WO 9635418; the bacterial peritonitis model of Sharar et al. (*J. Immunol.* 151:4982, 1993), the colitis model of Meenan et al. (*Scand. J. Gastroenterol.* 31:786, 1996), and the diabetes model of von Herrath et al. (*J. Clin. Invest.* 98:1324, 1996). Models for septic shock are described in Mack et al. *J. Surg. Res.* 69:399, 1997; and Seljelid et al. *Scand. J. Immunol.* 45:683-7.

For use as an active ingredient in a pharmaceutical preparation, a polypeptide, polynucleotide, or antibody of this invention is generally purified away from other reactive or potentially immunogenic components present in the mixture in which they are prepared. Typically, each active ingredient is provided in at least about 90% homogeneity, and more preferably 95% or 99% homogeneity, as determined by functional assay, chromatography, or SDS polyacrylamide gel electrophoresis. The active ingredient is then compounded into a medicament in accordance with generally accepted procedures for the preparation of pharmaceutical preparations, such as described in *Remington's Pharmaceutical Sciences 18th Edition* (1990), E.W. Martin ed., Mack Publishing Co., PA. Steps in the compounding of the medicament depend in part on the intended use and mode of administration, and may include sterilizing, mixing with appropriate non-toxic and non-interfering excipients and carriers, dividing into dose units, and enclosing in a delivery device. The medicament will typically be packaged with information about its intended use.

Mode of administration will depend on the nature of the condition being treated. For conditions that are expected to require moderate dosing and that are at well perfused sites (such as cardiac failure), systemic administration is acceptable. For example, the medicament may be formulated for intravenous administration, intramuscular injection, or absorption sublingually or intranasally. Where it is possible to administer the active ingredient locally, this is usually preferred. Local administration will both enhance the concentration of the active ingredient at the disease site, and minimize effects on TNF receptors on other tissues not involved in the disease process. Conditions that lend themselves to administration directly at the disease site include cancer and rheumatoid arthritis. Solid tumors can be injected directly when close to the skin, or when they can be reached by an endoscopic procedure. Active ingredients can also be administered to a tumor site during surgical resection, being implanted in a gelatinous matrix or in a suitable membrane such as Gliadel® (Guilford Sciences). Where direct administration is not possible, the administration may be given through an arteriole leading to the disease site. Alternatively, the pharmaceutical composition may be formulated to enhance accumulation of the active ingredient at the disease site. For example, the active ingredient can be encapsulated in a liposome or other matrix structure that displays an antibody or ligand capable of binding a cell surface protein on the target cell. Suitable targeting agents include antibodies against cancer antigens, ligands for tissue-specific receptors (e.g., serotonin for pulmonary targeting). For compositions that decrease TNF signal transduction, an appropriate targeting molecule may be the TNF ligand, since the target tissue may likely display an unusually high density of the TNF receptor.

Effective amounts of the compositions of the present invention are those that alter TRRE activity by at least about 10%, typically by at least about 25%, more preferably by about 50% or 75%. Where near complete ablation of TRRE activity is desirable, preferred compositions decrease TRRE activity by at least 90%. Where increase of TRRE activity is desirable, preferred compositions increase TRRE activity by at least 2-fold. A minimum effective amount of the

active compound will depend on the disease being treated, which of the TRRE modulators is selected for use, and whether the administration will be systemic or local. For systemic administration, an effective amount of activity will generally be an amount of the TRRE modulator that can cause a change in the enzyme activity by 100 to 50,000 Units — typically about 10,000 Units. The mass amount of protein, nucleic acid, or antibody is chosen accordingly, based on the specific activity of the active compound in Units per gram.

The following examples provided as a further guide to the practitioner, and are not intended to limit the invention in any way.

EXAMPLES

Example 1: Assay system for TRRE activity.

This Example illustrates an assay system that measures TRRE activity on the human TNF-R in its native conformation in the cell surface membrane

Membrane-associated TNF-R was chosen as the substrate, as having microenvironment similar to that of the substrate for TRRE in vivo. Membrane-associated TNF-R also requires more specific activity, which would differentiate less-specific proteases. Cells expressing an elevated level of the p75 form of TNF-R were constructed by cDNA transfection into monkey COS-1 cells which express little TNF-R of either the 75 kDa or 55 kDa size.

The procedure for constructing these cells was as follows: cDNA of human p75 TNF-R was cloned from a λ gt10 cDNA library derived from human monocytic U-937 cells (Clontech Laboratories, Palo Alto, CA). The first 300 bp on both 5' and 3' ends of the cloned fragment was sequenced and compared to the reported cDNA sequence of human p75 TNF-R. The cloned sequence was a 2.3 kb fragment covering positions 58-2380 of the reported p75 TNF-R sequence, which encompasses the full length of the p75 TNF-R-coding sequence from positions 90-1475. The 2.3 kb p75 TNF-R cDNA was then subcloned into the multiple cloning site of the pCDNA3 eukaryotic expression vector. The

orientation of the p75 TNF-R cDNA was verified by restriction endonuclease mapping.

Figure 1 illustrates the final 7.7 kb construct, pCDTR2. It carries the neomycin-resistance gene for the selection of transfected cells in G418, and the expression of the p75 TNF-R is driven by the cytomegalovirus promoter. The pCDTR2 was then transfected into monkey kidney COS-1 cells (ATCC CRL-1650) using the calcium phosphate-DNA precipitation method. The selected clone in G418 medium was identified and subcultured. This clone was given the designation **C75R**.

To determine the level of p75 TNF-R expression on C75R cells, 2×10^5 cells/well were plated into a 24-well culture plate and incubated for 12 to 16 hours in 5% CO₂ at 37°C. They were then incubated with 2-30 ng ¹²⁵I human recombinant TNF (radiolabeled using the chloramine T method) in the presence or absence of 100-fold excess of unlabeled human TNF at 4°C for 2 h. After three washes with ice-cold PBS, cells were lysed with 0.1N NaOH and bound radioactivity was determined in a Pharmacia Clinigamma counter (Uppsala, Sweden).

Figure 2 shows the results obtained. C75R had a very high level of specific binding of radiolabeled ¹²⁵I-TNF, while parental COS-1 cells did not. The number of TNF-R expressed on C75R was determined to be 60,000-70,000 receptors per cell by Scatchard analysis (Figure 2, inset). The K_d value calculated was 5.6×10^{-10} M. This K_d value was in close agreement to the values previously reported for native p75 TNF-R.

TRRE was obtained by PHA stimulation of THP-1 cells (WO 9802140). THP-1 cells (ATCC 45503) growing in logarithmic phase were collected and resuspended to 1×10^6 cells/ml of RPMI-1640 supplemented with 1% FCS and incubated with 10^{-6} M PMA for 30 min in 5% CO₂ at 37 °C. The cells were collected and washed once with serum-free medium to remove PMA and resuspended in the same volume of RPMI-1640 with 1% FCS. After 2 hours incubation in 5% CO₂ at 37°C, the cell suspension was collected, centrifuged, and the cell-free supernatant was collected as the source of TRRE.

In order to measure the effect of TRRE on membrane-bound TNF-R in the COS-1 cell constructs, the following experiment was performed. C75R cells were seeded at a density of 2×10^5 cells/well in a 24-well cell culture plate and incubated for 12 to 16 hours at 37°C in 5% CO₂. The medium in the wells was aspirated, replaced with fresh medium alone or with TRRE medium, and incubated for 30 min at 37°C. The medium was then replaced with fresh medium containing 30 ng/ml ¹²⁵I-labeled TNF. After 2 hours at 4°C, the cells were lysed with 0.1 N NaOH and the level of bound radioactivity was measured. The level of specific binding of C75R by ¹²⁵I-TNF was significantly decreased after incubation with TRRE. The radioactive count was 1,393 cpm on the cells incubated with TRRE compared to 10,567 cpm on the cells not treated with TRRE, a loss of 87% of binding capacity.

In order to determine the size of the p75 TNF-R cleared from C75R by TRRE, the following experiment was performed. 15×10^6 C75R cells were seeded in a 150 mm cell culture plate and incubated at 37°C in 5% CO₂ for 12 to 16 hours. TRRE medium was incubated with C75R cells in the 150 mm plate for 30 min and the resulting supernatant was collected and centrifuged. The concentrated sample was applied to 10% acrylamide SDS-PAGE and electrophoretically transferred to a polyvinylidene difluoride membrane (Immobilon). Immunostaining resulted in a single band of 40 kDa, similar to the size found in biological fluids. Thus, transfected COS-1 cells expressed high levels of human p75 TNF-R in a form similar to native TNF-R.

The following assay method was adopted for routine measurement of TRRE activity. C75R cells and COS-1 cells were seeded into 24-well culture plates at a density of 2.5×10^5 cells/ml/well and incubated overnight (for 12 to 16 hours) in 5% CO₂ at 37°C. After aspirating the medium in the well, 300 µl of TRRE medium was incubated in each well of both the C75R and COS-1 plates for 30 min in 5% CO₂ at 37°C (corresponding to A and C mentioned below, respectively). Simultaneously, C75R cells in 24-well plates were also incubated with 300 µl of fresh medium or buffer. The supernatants were collected,

centrifuged, and then assayed for the concentration of soluble p75 TNF-R by ELISA.

ELISA assay for released TNF-R (WO 9802140) was performed as follows: Polyclonal antibodies to human p75 TNF-R were generated by immunization of New Zealand white female rabbits (Yamamoto et al. *Cell. Immunol.* 38:403-416, 1978). The IgG fraction of the immunized rabbit serum was purified using a protein G (Pharmacia Fine Chemicals, Uppsala, Sweden) affinity column (Ey et al. (1978) *Immunochemistry* 15:429-436, 1978). The IgG fraction was then labeled with horseradish peroxidase (Sigma Chemical Co., St. Louis, MO) (Tijssen and Kurstok, *Anal. Biochem.* 136:451-457, 1984). In the first step of the assay, 5 µg of unlabeled IgG in 100 µl of 0.05 M carbonate buffer (pH 9.6) was bound to a 96-well ELISA microplate (Corning, Corning, NY) by overnight incubation at 4°C. Individual wells were washed three times with 300 µl of 0.2% Tween-20 in phosphate buffered saline (PBS). The 100 µl of samples and recombinant receptor standards were added to each well and incubated at 37°C for 1 to 2 hours. The wells were then washed in the same manner, 100 µl of horseradish peroxidase-labeled IgG added and incubated for 1 hour at 37 °C. The wells were washed once more and the color was developed for 20 minutes (min) at room temperature with the substrates ABTS (Pierce, Rockford, IL) and 30% H₂O₂ (Fisher Scientific, Fair Lawn, NJ). Color development was measured at 405 nm.

When C75R cells were incubated with TRRE medium, soluble p75 TNF-R was released into the supernatant which was measurable by ELISA. The amount of receptors released corresponded to the amount of TRRE added. There was also a level of spontaneous TNF-R release in C75R cells incubated with just medium alone. It is hypothesized that this is due to an endogenous source of proteolytic enzyme, a homolog of the human TRRE of monkey origin.

The following calculations were performed. A = (amount of soluble p75 TNF-R in a C75R plate treated with the TRRE containing sample); i.e. the total amount of sTNF-R in a C75R plate. B = (amount of soluble p75 TNF-R spontaneously released in a C75R plate treated with only medium or buffer

containing the same reagent as the corresponding samples but without exogenous TRRE); i.e. the spontaneous release of sTNF-R from C75R cells. C = (amount of soluble p75 TNF-R in a COS-1 plate treated with the TRRE sample or the background level of soluble p75 TNF-R released by THP-1.); i.e. the degraded value of transferred (pre-existing) sTNF-R in the TRRE sample during 30 min incubation in a COS-1 plate. This corresponds to the background level of sTNF-R degraded in a C75R plate. The net release of soluble p75 TNF-R produced only by TRRE activity existing in the initial sample is calculated as follows: (Net release of soluble p75 TNF-R only by TRRE) = A - B - C.

Unit activity of TRRE was defined as follows: 1 pg of soluble p75 TNF-R net release (A-B-C) in the course of the assay is one unit (U) of TRRE activity.

Using this assay, the time course of receptor shedding by TRRE was measured in the following experiment. TRRE-medium was incubated with C75R and COS-1 cells for varying lengths of time. The supernatants were then collected and assayed for the level of soluble p75 TNF-R by ELISA and the net TRRE activity was calculated. Detectable levels of soluble receptor were released by TRRE within 5 min and increased up to 30 min. Longer incubation times showed that the level of TRRE remained relatively constant after 30 min, presumably from the depletion of substrates. Therefore, 30 min was determined to be the optimal incubation time.

The induction patterns of TRRE and known MMPs by PMA stimulation are quite different. In order to induce MMPs, monocytic U-937 cells, fibrosarcoma HT-1080 cells, or peritoneal exudate macrophages (PEM) usually have to be stimulated for one to three days with LPS or PMA. On the other hand, as compared with this prolonged induction, TRRE is released very quickly in culture supernatant following 30 min of PMA-stimulation. The hypothesis that TRRE and sTNF-R form a complex *in vitro* was confirmed by the experiment that 25% TRRE activity was recovered from soluble p75 TNF-R affinity column. This means that free TRRE has the ability to bind to its catalytic product, sTNF-R.

The remaining 75% which did not combine to the affinity column may already be

bound to sTNF-R or may not have enough affinity to bind to sTNF-R even though it is in a free form.

Example 2: Characterization of TRRE obtained from THP-1 cells.

5 TRRE obtained by PHA stimulation of THP-1 cells was partially purified from the culture medium (WO 9802140). First, protein from the medium was concentrated by 100% saturated ammonium sulfate precipitation at 4°C. The precipitate was pelleted by centrifugation at 10,000 x g for 30 min and resuspended in PBS in approximately twice the volume of the pellet. This
10 solution was then dialyzed at 4°C against 10 mM Tris-HCl, 60 mM NaCl, pH 7.0. This sample was loaded on an anion-exchange chromatography, Diethylaminoethyl (DEAE)-Sephadex A-25 column (Pharmacia Biotech) (2.5 x 10 cm) previously equilibrated with 50 mM Tris-HCl, 60 mM NaCl, pH 8.0. TRRE was then eluted with an ionic strength linear gradient of 60 to 250 mM
15 NaCl, 50 mM Tris-HCl, pH 8.0. Each fraction was measured for absorbance at 280 nm and assayed for TRRE activity. The DEAE fraction with the highest specific activity (the highest value of TRRE units/A280) was pooled and used in the characterizations of TRRE described in this example.

In the next experiment, the substrate specificity of the enzyme was
20 elucidated using immunohistochemical techniques. Fluorescein isothiocyanate (FITC)-conjugated anti-CD54, FITC-conjugated goat anti-rabbit and mouse antibodies, mouse monoclonal anti-CD30, anti-CD11b and anti-IL-1R (Serotec, Washington D.C.) were used. Rabbit polyclonal anti-p55 and p75 TNF-R were obtained according to Yamamoto et al. (1978) *Cell Immunol.* 38:403-416. THP-
25 1 cells were treated for 30 min with 1,000 and/or 5,000 U/ml of TRRE eluted from the DEAE-Sephadex column, and then transferred to 12 x 75 mm polystyrene tubes (Fischer Scientific, Pittsburgh, PA) at 1×10^5 cells/100 μ l/tube. The cells were then pelleted by centrifugation at 350 x g for 5 min at 4°C and stained directly with 10 μ l FITC-conjugated anti-CD54 (diluted in cold PBS/0.5% sodium
30 aside), indirectly with FITC-conjugated anti-mouse antibody after treatment of

mouse monoclonal anti-CD11b, IL-1R and CD30 and also indirectly with FITC-conjugated anti-rabbit antibody after treatment of rabbit polyclonal anti-p55 and p75 TNF-R.

- THP-1 cells stained with each of the antibodies without treatment of TRRE
- 5 were used as negative controls. The tubes were incubated for 45 min at 4°C, agitated every 15 min, washed twice with PBS/2% FCS, repelleted and then resuspended in 200µl of 1% paraformaldehyde. These labeled THP-1 cells were analyzed using a fluorescence activated cell sorter (FACS) (Becton-Dickinson, San Jose, CA) with a 15 mW argon laser with an excitation of 488 nm.
- 10 Fluorescent signals were gated on the basis of forward and right angle light scattering to eliminate dead cells and aggregates from analysis. Gated signals (10^4) were detected at 585 BP filter and analyzed using Lysis II software. Values were expressed as percentage of positive cells, which was calculated by dividing mean channel fluorescence intensity (MFI) of stained THP-1 cells
- 15 treated with TRRE by the MFI of the cells without TRRE treatment (negative control cells).

- To test the *in vitro* TNF cytolytic assay by TRRE treatment the L929 cytolytic assay was performed according to the method described by Gatanaga et al. (1990b). Briefly, L929 cells, an adherent murine fibroblast cell line, were
- 20 plated (70,000 cells/0.1ml/well in a 96-well plate) overnight. Monolayered L929 cells were pretreated for 30 min with 100, 500 or 2,500 U/ml of partially-purified TRRE and then exposed to serial dilutions of recombinant human TNF for 1 hour. After washing the plate with RPMI-1640 with 10% FCS to remove the TRRE and TNF, the cells were incubated for 18 hours in RPMI-1640 with 10%
- 25 FCS containing 1 µg/ml actinomycin D at 37°C in 5% CO₂. Culture supernatants were then aspirated and 50 µl of 1% crystal violet solution was added to each well. The plates were incubated for 15 min at room temperature. After the plates were washed with tap water and air-dried, the cells stained with crystal violet were lysed by 100 µl per well of 100 mM HCl in methanol. The absorbance at

550 nm was measured using an EAR 400 AT plate reader (SLT-Labinstruments, Salzburg, Austria).

To investigate whether TRRE also truncates the ~55 kDa size of TNF-R, partially-purified TRRE was applied to THP-1 cells which express low levels of both p55 and p75 TNF-R (approximately 1,500 receptors/cell by Scatchard analysis). TRRE eluate from the DEAE-Sephadex column was added to THP-1 cells (5×10^6 cells/ml) at a final TRRE concentration of 1,000 U/ml for 30 min. The concentration of soluble p55 and p75 TNF-R in that supernatant was measured by soluble p55 and p75 TNF-R ELISA. TRRE was found to truncate both human p55 and p75 TNF-R on THP-1 cells and released 2,382 and 1,662 pg/ml soluble p55 and p75 TNF-R, respectively.

Therefore, TRRE obtained by PHA stimulation of THP-1 cells is capable of enzymatically cleaving and releasing human p75 TNF-R on C75R cells, and both human p55 and p75 TNF-R on THP-1 cells.

Partial inhibition of TRRE activity was obtained by chelating agents such as 1,10-phenanthroline, EDTA and EGTA (% TRRE activity remaining were 41%, 67% and 73%, respectively, at 2 mM concentration). On the other hand, serine protease inhibitors such as PMSF, AEBSF and 3,4-DCI, and serine and cysteine protease inhibitors such as TLCK and TPCK had no effect on the inhibition of TRRE. TRRE was slightly activated in the presence of Mn^{2+} , Ca^{2+} , Mg^{2+} , and Co^{2+} (% TRRE activities remaining were 157%, 151%, 127%, and 123%, respectively), whereas partial inhibition occurred in the presence of Zn^{2+} and Cu^{2+} (% TRRE activities remaining were 23% and 47%, respectively) (WO 9802140).

TRRE fractions from the most active DEAE fraction (60 mM to 250 mM NaCl) can be purified further. In one method (WO 9802140), the fractions were concentrated to 500 μ L with a Centriprep-10 filter (10,000 MW cut-off membrane) (Amicon). This concentrated sample was applied to 6% PAGE under non-denaturing native conditions. The gel was sliced horizontally into 5 mm strips and each was eluted into 1 ml PBS. The eluates were then tested according to the assay (Example 1) for TRRE activity.

Example 3: TRRE activity alleviates septic shock

The following protocol was used to test the effects of TRRE in preventing mortality in a model for septic shock. Mice were injected with lethal or sublethal levels of LPS, and then with a control buffer or TRRE. Samples of peripheral blood were then collected at intervals to establish if TRRE blocked TNF-induced production of other cytokines in the bloodstream. Animals were assessed for the ability of TRRE to block the clinical effects of shock, and then euthanized and tissues examined by histopathological methods.

Details were as follows: adult Balb/c mice, were placed in a restraining device and injected intravenously via the tail vein with a 0.1 ml solution containing 10 ng to 10 mg of LPS in phosphate buffer saline (PBS). These levels of LPS induce mild to lethal levels of shock in this strain of mice. Shock results from changes in vascular permeability, fluid loss, and dehydration, and is often accompanied by symptoms including lethargy, a hunched, stationary position, rumped fur, cessation of eating, cyanosis, and, in serious cases, death within 12 to 24 hours. Control mice received an injection of PBS. Different amounts (2,000 or 4,000 U) of purified human TRRE were injected IV in a 0.1 ml volume within an hour prior to or after LPS injection. Serum (0.1 ml) was collected with a 27 gauge needle and 1 ml syringe IV from the tail vein at 30, 60 and 90 minutes after LPS injection. This serum was heparinized and stored frozen at -20°C. Samples from multiple experiments were tested by ELISA for the presence of sTNF-R, TNF, IL-8 and IL-6. Animals were monitored over the next 12 hours for the clinical effects of shock. Selected animals were euthanized at periods from 3 to 12 hours after treatment, autopsied and various organs and tissues fixed in formalin, imbedded in paraffin, sectioned and stained by hematoxylin-eosin (H and E). Tissue sections were subjected to histopathologic and immunopathologic examination.

Figure 3 shows the results obtained. (♦) LPS alone; (■) LPS plus control buffer; (●) LPS plus TRRE (2,000 U); (▲) LPS plus TRRE (4,000 U).

Mice injected with LPS alone or LPS and a control buffer died shortly after injection. 50% of the test animals were dead after 8 hours (LPS) or 9 hours (LPS plus control buffer), and 100% of the animals were dead at 15 hours. In contrast, animals treated with TRRE obtained as described in Example 1 did much better.

5 When injections of LPS were accompanied by injections of a 2,000 U of TRRE, death was delayed and death rates were lower. Only 40% of the animals were dead at 24 hours. When 4,000 U of TRRE was injected along with LPS, all of the animals had survived at 24 hours. Thus, TRRE is able to counteract the mortality induced by LPS in test animals.

10 Example 4: TRRE activity decreases tumor necrotizing activity

The following protocol was followed to test the effects of TRRE on tumor necrosis in test animals in which tumors were produced, and in which TNF was subsequently injected.

15 On Day 0, cutaneous Meth A tumors were produced on the abdominal wall of fifteen BALB/c mice by intradermal injection of 2×10^5 Meth A tumor cells. On Day 7, the mice were divided into three groups of five mice each and treated as follows:

- Group 1: Injected intravenously with TNF (1 μ g/mouse).
- 20 • Group 2: Injected intravenously with TNF (1 μ g/mouse) and injected intratumorally with TRRE obtained as in Example 1 (400 units/mouse, 6, 12 hours after TNF injection).
- Group 3: Injected intravenously with TNF (1 μ g/mouse) and injected intratumorally with control medium (6, 12 hours after TNF injection).

25 On Day 8, tumor necrosis was measured with the following results: Group 1: 100% of necrosis (5/5); Group 2: 20% (1/5); Group 3: 80% (4/5). Injections of TRRE greatly reduced the ability of TNF to induce necrosis in Meth A tumors in BALB/c mice.

Since adding TRRE activity ablates the beneficial necrotizing activity of TNF, blocking endogenous TRRE activity would promote the beneficial effects of TNF.

5 **Example 5: Nine new polynucleotide clones that affect TRRE activity**

A number of cells have been found to express high levels of TRRE activity, especially after PMA stimulation. These include the cell lines designated THP-1, U-937, HL-60, ME-180, MRC-5, Raji, K-562. Jurkat cells have a high TRRE activity (850 TRRE U/mL at 10^{-2} PMA). In this experiment, the expression
10 library of the Jurkat T cell (ATCC #TIB-152) was obtained and used to obtain 9 polynucleotide clones that augment TRRE activity.

Selection of expression sequences in the library was done by repeated cycles of transfection into COS-1 cells, followed by assaying of the supernatant as in Example 1 for the presence of activity cleaving and releasing the TNF
15 receptor. Standard techniques were used in the genetic manipulation. Briefly, the DNA of 10^6 Jurkat cells was extracted using an InVitrogen plasmid extraction kit according to manufacturer's directions. cDNA was inserted in the ZAP Express™/EcoRI vector (cat. no. 938201, Stratagene, La Jolla CA. The library was divided into 48 groups of DNA and transformed into COS-1 cells using the
20 CaCl transfection method. Once the cells were grown out, the TRRE assay was performed, and five positive groups were selected. DNA from each of these five groups was obtained, and transfected into *E. coli*, with 15 plates per group. DNA was prepared from these cells and then transfected into COS-1 cells once more. The cells were grown out, and TRRE activity was tested again. Two positive
25 groups were selected and transfected into *E. coli*, yielding 98 colonies. DNA was prepared from 96 of these colonies and transfected into COS-1 cells. The TRRE activity was performed again, and nine clones were found to substantially increase TRRE activity in the assay. These clones were designated 2-8, 2-9, 2-14, 2-15, P2-2, P2-10, P2-13, P2-14, and P2-15.

30 **Figure 4** is a bar graph showing the TRRE activity observed when the 9 clones were tested with C75 cells in the standard assay (Example 1).

These nine clones were then sequenced according to the following procedure:

1. Plasmid DNA was prepared using a modified alkaline lysis procedure.
2. DNA sequencing was performed using DyeDeoxy termination reactions (ABI). Base-specific fluorescent dyes were used as labels.
3. Sequencing reactions were analyzed on 5.75% Long Ranger™ gels by an ABI 373A-S or on 5.0% Long Ranger™ gels by an ABI 377 automated sequencer.
4. Subsequent data analysis was performed using Sequencher™ 3.0 software.

Standard primers T7X, T3X, -40, -48 Reverse, and BK Reverse (BKR) were used in sequencing reactions. For each clone, several additional internal sequencing primers (listed below) were synthesized.

NCBI BLAST (Basic Local Alignment Search Tool) sequence analysis (Altschul et al. (1990) *J. Mol. Biol.* 215:403-410) was performed to determine if other sequences were significantly similar to these sequences. Both the DNA sequences of the clones and the corresponding ORFs (if any) were compared to sequences available in databases.

The following clones were obtained and sequenced:

Clone	Sequence Designation	SEQ ID NO.	Approximate Length (bp)	Expression Designation	Related sequences (potential homology)
2-9	AIM2	1	4,047		—
2-8	AIM3T3 (partial sequence)	2	739		<i>M. musculus</i> 45S pre-rRNA gene
	AIM3T7 (partial sequence)	3	233		
2-14	AIM4	4	2,998	Mey3	human arfaptin 2 and others (see below)
2-15	AIM5	5	4,152		—
P2-2	AIM6	6	3,117	Mey5	—
P2-10	AIM7	7	3,306	Mey6	Human Insulin-like Growth factor II Receptor
P1-13	AIM8	8	4,218		—
P2-14	AIM9	9	1,187	Mey8	—
P2-15	AIM10	10	3,306		E1b-55kDa-associated protein

5

sequencing are shown in SEQ. ID NOS:39-46. The sequences of AIM3T3 and

AIM3T7 are presented in SEQ ID NOS:2 and 3, respectively. The BLAST search revealed that the AIM3T3 sequence may be homologous to the mouse (*M. musculus*) 28S ribosomal RNA (Hassouna et al. *Nucleic Acids Res.* 12:3563-3583, 1984) and the *M. musculus* 45S pre-rRNA genes (Accession No. X82564.

5 The complementary sequence of the AIM3T3 sequence showed 99% similarity over 408 bp beginning with nt 221 of SEQ ID NO:2 to the former and 97% similarity over the same span to the latter.

Clone 2-14 (AIM4). The internal primers used for sequencing are shown in SEQ. ID NOS:14-65. The sequence of AIM4 is presented in SEQ ID NO:4. The
10 complementary strand of the AIM4 sequence is SEQ ID NO:149. The longest ORF in the AIM4 sequence is 236 AA long and represented in SEQ ID NO:150. AIM4 has significant alignments to human sequences arfaptin 2, ADE2H1 mRNA showing homologies to SAICAR synthetase, polypyrimidine tract binding protein (heterogeneous nuclear ribonucleoprotein I) mRNA, several PTB genes for
15 polypirimidine tract binding proteins, mRNA for por1 protein. Human arfaptin 2 is a putative target protein of ADP-ribosylation factor that interacts with RAC1 by binding directly to it. RAC1 is involved in membrane ruffling. Arfaptin 2 has possible transmembrane segments, potential CK2 phosphorylation sites, PKC phosphorylation site and RGD cell attachment sequence.

20 *Clone 2-15 (AIM5):* The internal primers used for sequencing are shown in SEQ. ID NOS:66-80. The sequence of AIM5 is presented in SEQ ID NO:5. The BLAST search revealed that the AIM5 sequence displays some similarity to Human Initiation Factor 5A (eIF-5A) Koettwitz et al. (1995) *Gene* 159:283-284, 1995 and Human Initiation Factor 4D (eIF 4D) Smit-McBride et al. (1989) *J. Biol.*
25 *Chem.* 264:1578-1583, 1989.

Clone P2-2 (AIM6): The internal primers used for sequencing are shown in SEQ. ID NOS:81-93. The sequence of AIM6 is presented in SEQ ID NO:6. The longest ORF in the AIM6 sequence is 1038 AA long and represented in SEQ ID NO:151.

30 *Clone P2-10 (AIM7):* The internal primers used for sequencing are shown in SEQ. ID NOS:94-106. The sequence of AIM7 is presented as SEQ ID NO:7.

The longest ORF in the AIM7 sequence is 849 AA long and represented in SEQ ID NO:152. The BLAST search revealed that this clone may be related to the Human Insulin-like Growth Factor II Receptor (Morgan et al. *Nature* 329:301-307, 1987 or the Human Cation-Independent Mannose 6-Phosphate Receptor mRNA (Oshima et al. *J. Biol. Chem.* 263:2553-2562, 1988). The AIM7 sequence showed roughly 99% identity to both sequences over 2520 nucleotides beginning with nt 12 of SEQ ID NO:7 and 99% similarity to the latter over the same span.

Clone P2-13 (AIM8): The internal primers used for sequencing are shown in SEQ. ID NOS:107-118. The sequence of AIM8 is presented as SEQ ID NO:8. The longest ORF in the AIM8 sequence is 852 AA long and represented in SEQ ID NO:153.

Clone P2-14 (AIM9): The internal primers used for sequencing are shown in SEQ. ID NOS:119-124. The sequence of AIM9 is presented as SEQ ID NO:9. The longest ORF was about 149 amino acids in length.

Clone P2-15 (AIM10): The internal primers used for sequencing are shown in SEQ. ID NOS:125-146. The sequence of AIM10 is presented as SEQ ID NO:10. The longest ORF in the AIM10 sequence is 693 AA long and represented in SEQ ID NO:154. Sequence 10 on BLASTN search of non-redundant databases at NCBI aligns with Human mRNA for E1b-55kDa-associated protein, locus HSA7509 (Accession AJ007509, NID g3319955).

Clonal DNA may be directly injected into test animals in order to test the ability of these nucleic acids to induce TRRE activity, counteract septic shock and/or affect tumor necrosis, as is described in detail in Examples 3 and 4. Alternatively, proteins or RNA can be generated from the clonal DNA for similar testing.

Example 6: Expression of newly obtained clones

Example 5 describes 9 new clones which enhance TRRE activity in a cell surface assay system. The clones were obtained in the pBK-CMB Phagmid vector.

The following work was done on contract through the commercial laboratory Lark Technologies, Houston, TX. The clones were removed from shuttle vectors and inserted into expression vectors in the following manner. Recombinant plasmid (pBK-CMV containing insert) was digested with appropriate restriction enzyme(s) such as Spe I, Xba I, EcoR I or others, as appropriate. The Baculovirus Transfer Vector (pAcGHLT-A Baculovirus Transfer Vector, PharMingen, San Diego, CA, Cat. No. 21460P) was also cut with appropriate restriction enzyme(s) within or near the multiple cloning site to receive the insert removed from the shuttle vector.

The fragment of interest being subcloned was isolated from the digest using Low-Melting agarose electrophoresis and purified from the gel using a Qiaquick Gel Extraction Kit following Lark SOP MB 020602. If necessary, the receiving vector was treated with alkaline phosphatase according to Lark SOP MB 090201. The fragment was ligated into the chosen site of the vector pAcGHLT-A. The recombinant plasmid was transformed into *E. coli* XL1 Blue MRF⁺ cells and the transformed bacterial cells were selected on LB agar plates containing ampicillin (100µg/ml). Ampicillin resistant colonies were picked and grown on LB broth containing ampicillin for plasmid preparation.

Plasmid DNA was prepared using Alkaline Miniprep Procedure (Lark SOP MB 010802 and digested with appropriate restriction enzyme(s). Selected subclones were confirmed to be of the correct size. Subclones were digested with other appropriate restriction enzyme(s) to ascertain correct orientation of the insert by confirming presence of fragments of proper size(s). A subclone was grown in 100 ml of LB broth containing ampicillin (100µg/ml) and the plasmid DNA prepared using Qiagen Midi Plasmid Preparation Kit (Lark SOP MB 011001). The DNA concentration was determined by measuring the absorbance at 260 nm and the DNA sample was verified to be originated from correct subclone by restriction digestion.

Thus were produced the expression constructs for Mey3, Mey5, Mey6, Mey8 now with the coding sequence of interest fused to GST gene with polyhistidine tag, protein kinase A site and thrombin cleavage site. The GST

gene and now the fusion protein are under the polyhedrin promotor. PharMingen (San Diego, CA) incorporated the vector with insert into functional baculovirus particles by co-inserting the transfer vector (pAcGHLT) into susceptible insect cell line S along with linearized virus DNA (PharMingen, San Diego, CA, BaculoGold viral DNA, Cat. No. 21100D). The functional virus particles were grown again on the insect cells to generate a high titer stock. Protein production was then done by infecting a large culture of cells in Tini cell. The cells were harvested when the protein yield reached a maximum and before the virus killed the cells. Fusion proteins were collected on a glutathione-agarose column, washed and released with glutathionine.

Proteins collected from the affinity column were quantified by measuring OD₂₈₀ and were assayed on gels using SDS-PAGE and Western blotting with labeled anti-GST (PharMingen, San Diego, CA, mAbGST Cat. No. 21441A) to confirm that all the bands present included the GST portion.

Four of the ten sequences have been cloned, expressed in baculovirus infected insect cells, and then purified.

TABLE 2: Expressed protein from Jurkat library clones		
Name	Sequence in insert	Amount of protein (mg/mL)
Mey3	AIM4	4.7, 5.0
Mey5	AIM6	1.36, 1.50
Mey6	AIM7	0.33
Mey8	AIM9	1.53

Gels indicated the presence of the GST protein in addition to larger proteins that were also positive with the anti-GST antibody in Western analyses. Mey3 repeatedly exhibited the presence of proteins around 32kDa, 56kDa, bands around 60-70kDa and another larger than 70kDa. Mey5 consistently had proteins migrating as approximately 34kDa, 38kDa, 58kDa, around 60-70kDa, and others larger than 70kDa. Mey6 had protein bands around 34kDa, 56kDa,

58kDa, and bands around 60-70kDa. Mey8 had protein bands around 36kDa, 58kDa and bands around 60-70kDa. All of the indicated bands were positive for GST. The bands may represent the desired fusion protein or degradation/cleavage product generated during growth and purification.

5

Example 7: Assay of expression products for effect on TNF-R cleaving activity

The following method was used to measure TRRE activity of Mey 3, 5, 6 and 8. C75R cells and COS-1 cells were seeded into 24-well culture plates at a density of 2.5×10^5 cells/ml/well and incubated overnight (for 12 to 16 hours) in 10 5% CO₂ at 37°C. After aspirating the medium in the well, 300μl of 1 ug of Mey 3, 5 and 8 were incubated in each well of both the C75R and COS-1 plates for 30 min in 5% CO₂ at 37°C (corresponding to A and C mentioned below, respectively). Simultaneously, C75R cells in 24-well plates were also incubated with 300μl of fresh medium or buffer (corresponding to B mentioned below). The 15 supernatants were collected, centrifuged, and then assayed for the concentration of soluble p75 TNF-R by ELISA as described in Example 1.

The following results were obtained:

TABLE 3: Enzymatic activity of expressed clones	
Clone No.	TNF-receptor releasing activity U/mg
Mey-3	341
Mey-5	671
Mey-6	452
Mey-8	191

20

Example 8: Effectiveness of expression products in treating septic shock

The protocol outlined in Example 3 was used to test the effects of the expression products from the new clones in preventing mortality in the septic shock model.

- 5 Different amounts of recombinant Mey 3, 5, and 8 (10 – 100 ug/mouse) were injected i.v. in a 0.05 ml volume within an hour prior to or after injection of a lethal dose of LPS. Serum (0.1ml) was collected using a 27 gauge needle and 1 ml syringe from the tail vein at 30, 60 and 90 minutes after LPS injection. This serum was heparinized and stored frozen at -20°C. Samples from multiple
10 experiments were tested by ELISA for the presence of solubilized TNF-R, the TNF ligand, IL-8, and IL-6. Animals were monitored over the next 12 hours for the clinical effects of shock. Selected animals were euthanized from 3 to 12 hours after treatment, autopsied and various organs and tissues fixed in formalin, imbedded in paraffin, sectioned and stained by hematoxylin-eosin (H and E).
15 Tissue sections were subjected to histopathologic and immunopathologic examination.

Figure 5 shows the results obtained. (♦) saline; (■) BSA; (Δ) Mey-3 (100 µg); (X) Mey-3 (10 µg); (*) Mey-5 (10 µg); (●) Mey-8 (10 µg).

- Mice injected with LPS alone or LPS, a control buffer or control protein
20 (BSA) died rapidly. All of the animals in this group were dead at 24 hours. In contrast, when injections of LPS were accompanied by injections of a 10 – 100 µg of Mey 3, 5 and 8, death was delayed and death rates were lower. None of the animal were dead at 24 hours that had been treated with Mey 3 and Mey 5. Only 66 % of the animals were dead at 24 hours that had been treated with Mey
25 8. Thus, Mey 3, 5 and 8 were able to counteract the mortality induced by LPS in test animals.

SEQUENCE LISTING

(1) GENERAL INFORMATION:

- (i) APPLICANT: Gatanaga, T.
Granger, G.A.
- (ii) TITLE OF INVENTION: Factors Altering Tumor Necrosis
Factor Receptor Releasing Enzyme Activity
- (iii) NUMBER OF SEQUENCES: 154

(iv) CORRESPONDENCE ADDRESS:

- (A) ADDRESSEE: MORRISON & FOERSTER
(B) STREET: 755 PAGE MILL ROAD
(C) CITY: Palo Alto
(D) STATE: CA
(E) COUNTRY: USA
(F) ZIP: 94304-1018

(v) COMPUTER READABLE FORM:

- (A) MEDIUM TYPE: Diskette
(B) COMPUTER: IBM Compatible
(C) OPERATING SYSTEM: Windows
(D) SOFTWARE: FastSEQ for Windows Version 2.0b

(vi) CURRENT APPLICATION DATA:

- (A) APPLICATION NUMBER:
(B) FILING DATE:
(C) CLASSIFICATION:
- (vii) PRIOR APPLICATION DATA:
(A) APPLICATION NUMBER: USSN 09/081,385
(B) FILING DATE: 014-NOV-1998

(viii) ATTORNEY/AGENT INFORMATION:

- (A) NAME:
(B) REGISTRATION NUMBER:
(C) REFERENCE/DOCKET NUMBER: 22000-20577.21

(ix) TELECOMMUNICATION INFORMATION:

- (A) TELEPHONE: 650-813-5600
(B) TELEFAX: 650-494-0792
(C) TELEX: 706141

(2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 4047 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Genomic DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

AAGCTTTTTC	CTTTCTTCC	CCGGGAAGG	CCGGGCCAG	AGACCCGAC	TCGGACCAAG	60
CGGGGGCTGC	GGGGCCAGAG	TGGGCTGGG	AGGGCTGGG	GGCGCTCTGG	GGCCGGCTCC	120
TCCAGGCTGG	GGGGCCAG	CTCCGGGAAG	GCAGTCTGG	CCTGCGGATG	GGGCCCGGCG	180
TGGGGCCCGG	CGGGGCCGCG	TCGGGAGGCG	TCCAGGCTGC	GGGAGCGGGA	GGAGCGGCGG	240
TGCGGGCGCG	AGCGCCGTGG	GTGGAGGTGC	CGGTCCCTCC	TGAGGGGCGAG	CCAGTGGGTT	300
TGGGACCCGG	GAGCAGAGCC	CGCGCTCTCC	CAGCGGCTC	CCCGGGGTC	TCACCGGGTC	360
ACCCGAGAGC	GGAGGCCCGG	GCTCCGAGA	AACCCGGGCG	GGCCGCGGGG	AAGCAGCGCC	420
CTCAGGCGTC	GGAGGAGCCC	CCAGAAGGAG	CTCGGGCTTT	CCCGCGGGGG	TCCAGCGGCC	480
TGGGTTTCGT	CGGGGACGCG	CCAGGCCGCG	AGGACCCCCA	AGCGGAGCTC	AGTCTCGGGG	540
GCACGACCCA	GAGGCCAGCA	CCAGAGGAGC	GGGGCGGGCG	GGGAGAGGGG	CGGGGAGGGG	600
GCTCTCGGGA	GCTCAGGGCC	AGGGCTAGAC	TTTCAAGGTC	ATGGCTGGG	CCCTCATCCG	660
CAGGGAGGTG	AGGGGGCTCT	GTGACAGAG	GGGGGCCCGG	TGAGGAAGGC	GCTGCTAGCC	720

AGGGGCGGGG CAGGAGCCCA GGTGGGGACT TAAGGGTGGC TGAAGGGACC CTCAGGCTGC 780
 AGGGATAGGG AGGGAAGCTA GGGGTGTGGC TTGGGAGGCT GCGGGGGACC CGCGGGCGCC 840
 CTTTATTCTG AAGCCGAATG TGCTGCCGGA GTCCCAAGT ACCTAGAAAT CCATTTCAG 900
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 GAGATATGGG TGAAGAACCAG GAGAGAGGGA AGTCCCGGAG CGCGATGATG GGACAGAGAG 1020
 CGGGGACCAG AATTTTAA ACACGATCTG AGATGGCTTT GGCAGACTCA TAGTTGTTT 1080
 CTTTCACGG AGAAAGGTGG GGCAGAAGCC AGCTCTAAAG CCCAGGCTGC CCAGCCTGCA 1140
 TGGGACAGC TGAAGAAGG CCAGGGGAGA GCTTTCCCTC CTTGTACAG ACATGAGCC 1200
 TGGAATCTG GAATGGGCA GATGTGCCA GGGAAAGCTG ATCCGCCGCC ACCCAGGGCC 1260
 CGCCGGGTGC CCCTTTGAGC GTGGAACTGT TSCCAGTCA TGCTCCCTGC CTATCGAACA 1320
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 GTGAACCAA ATTTGCTGCT CTAAGGCCA AAAGGCAGTT CACCTCTCTG GCTATTCTG 3540
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 CTGTGCGGGG GGGGCTCCTT TGGATCC 4047

(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 739 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Genomic DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

GGATCCAAAG GTCAAACTCC CCACCTGGCA CTGTCCCCGG AGCGGGTGGC GCCCGGCGGG 60
 GCGCGGGCGG GGGGCTTGGC GCGAGAAGGG AGAGGCCCTC GGGGCTCGCG CCCCGCGCTC 120
 ACCGGGTCAG TGAAGAAAGC ATCAGAGTAG TGGTATTCCA CCGCGGCCCG CGAGGGCGGG 180
 CGGACCCCGG CCCGGCCCCC TCGCGGGGAC ACCGGGGGGG GCGCGGGGCG CTCCCACTTA 240

TTCTACACCT	CTCATGCTC	TTCACCGTGC	CAGACTAGAG	TCAAGCTCAA	CAGGGTCTTC	300
TTTCCCGCGT	GATTCGCCA	AGCCCGTTCC	CTTGGCTGTG	GTTTGCTGG	ATAGTAGGTA	360
GGGACAGTGG	GAATCTCGT	CATCCATCCA	TGCCTGCTAC	TAATTAGATG	ACGAGGCATT	420
TGGCTACCTT	AAGAGAGTCA	TAGTTACTCC	CGCGCTTTAC	CCGCGCTTCA	TGAATTTCT	480
TCACTTTGAC	ATTGAGAGCA	CTGGGCAGAA	ATCACATGCG	GTCAAACCC	GCCTGGGGC	540
TTGCGGTAGT	TTTGTTTTAA	TAAAGACTC	GGATTCCCTC	GGTCCGACC	AGTTCTAAGT	600
CGCGTCTAGT	CGCCGCGCG	AAGCGAGGCG	CGCGCGGAA	CGCGCGCCC	CGGGCGGGAC	660
CGCGGGGGG	GACCGGCGCG	CGGCCCTCTC	CGCCCTGCCC	CGCGCGCGCG	CGCGCGCGCG	720
CGGAAGAGA	AGGGGGAAA					739

(2) INFORMATION FOR SEQ ID NO:3:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 233 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Genomic DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

CAAGAGTGGC	GGCCGAGCA	GGCCCCCGG	GTGCCCGGGC	CCCCCTCGAG	GGGACAGTG	60
CCCCCGCGCG	GGGGGCCCC	CGCGGGCGCG	CGCGCGGCC	CTGCCCGCCC	GACCTTCTC	120
CCCCCGCGCG	CGCGCCGAC	CGCGCTCTCC	CGCGGGAGGG	GGGAGGACGG	GGAGCGGGGG	180
AGAGAGAGAG	AGAGAGAGG	CGCGGGGTGG	CTCGTGCCGA	ATTCAAAAAG	CTT	233

(2) INFORMATION FOR SEQ ID NO:4:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 2998 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Genomic DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

GGATCCAAAG	AATTCGGCAC	GAGGTAGTCA	CGGCTTGTGT	CATTGTTGTA	CTTGACGTG	60
AGGCTGTGTA	GCTTGGAAAA	GTGATGCGC	AGCGTGCAG	AGGCGTTGTA	GATGTTCTGC	120
CGGCTCAGCG	ACAGCTTGGC	GTGCTGGCC	CTACGGGGT	CGCATATAG	CAGCAGGGCC	180
TGGAACATGT	TGTTCTTGGT	GAAGGTGATG	ATCTTCAACA	CTGTGCGGAA	CTTGGAGAAA	240
ATCTGTGCGA	GCACATCCAG	GCTCAGAGG	TAGAAGAGTT	TCTCCAGAT	GATCCTGAGC	300
ACGGGGCTCT	GCCCAGCCAT	CGCATCCCT	GCATCCACGG	CGCGCCGCA	GGCAGCCAAG	360
GCCAGGTTGC	CCGACTGGAC	CGAGTTCACC	CGCTGCAGG	CGCGCTGGCG	CGCGCGCTGG	420
TTGGGAGAGC	TGTCGGTCTT	CAGCTCCTTG	TGGTTGGAGA	ACTGGATGTA	GATGGGCTGG	480
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GTGTTATCTT	CGATGAAGCG	CTGGTTTTC	CCCTTCACGA	TCAAGAGGTT	GGTGACCTTC	600
ATGTGGATCA	CTCTAGAGGG	GACGCTTCC	CCCTCGCTGA	CGTCGATGG	GAGCTTCGGG	660
TCATTTCCGT	TTGCTGCAGA	AGCCGAGTTG	CTGCTCATGA	TAAACGGTCC	GTTAGTGACA	720
CAGTAGAGAA	AAAGCTCGTC	AGATCCCCCG	TTTGTACCAA	CGGCTATATC	TGGGACAATG	780
CCGTCATAGT	CACACAGAGC	AGACCCGGGG	GGGACGGAGT	GGAGCGCGCG	GAATCCTGGA	840
GCTAGGAGTG	CAGATTGAGT	TGCTGCGTGA	GACGAAGCGC	AGATATGAGA	GTGCTCTGCA	900
CTGCGGCGGG	GCACGTGACG	CCACCTCTCA	CAGCTGTCTG	CAGACCCAGC	ATGCACTGGG	960
TGATGCCCTT	GCTGACCTCA	GCCAGAAAGT	CCGAGGACTT	CABGAGGAAT	TTGCTAGACA	1020
TGACAGAGCA	CAGAAACTAC	TATGCAAGAA	TGGGAAACCT	CTGCTAGGAG	CCGTGAAGCT	1080
CTTTGCTCTT	AGCATATACA	CATTTGCTAC	CAGAACCTAT	GAGACACAGC	TGCTGACTGT	1140
GAAACATAT	GAGGTCGCA	GCTTGGATAA	TGATGCTTAC	GACACAGACT	TAGAGAGACT	1200
GAGTCTAGCG	CCCGGGGATG	CAGGGACACG	TGCTGCACTT	GAGAGTGCCC	AGGCACTTTT	1260
CGAGGCCCAT	CGGGAACAAT	ATGAGAAGCT	CGCGGGAAGT	GTGGGCATCA	AGTCAAGTTT	1320
CTGGAAGAAA	ACAAGATACA	AGGTGATGCA	CAAGCAGCTG	CTGCTCTCC	ACAATGCTGT	1380
GTCCCGCTACT	TTTGTGGGA	ACCGAANAACA	GCTGGAGCAG	ACCTCTGACG	AGTTCACACT	1440
CAGCTGCGGG	CCTCCAGGAG	CTGAGAAGCC	CTCCTGGCTA	GAGGAGCAGT	GAGCTGCTCC	1500
CAGCCCAACT	TGCGTATCAA	GAAGACACTT	GGGAAGGACA	CGCCGAGGGT	GTGGGAGATT	1560
GGACATGGTA	CATCCTTTGT	CATCTGGAGT	CTGGCTTGGG	CTCCTTTTTC	TGCTGGGGCT	1620
CTGACACAG	TTTGGCCAG	ATTGCTATGG	TGGGAAGAGG	GCTCGAGGCG	CCAGAGTTGT	1680
CGCTGCTGTC	TATCTTCTGT	GCCACAGGCG	TTCAATCCCA	GATCTTTTTC	TTCACACTTA	1740
CAGCCACAGG	CTATGACAAA	ACCACCTCCCT	GGCCAAATGGC	ATCACTCTTC	AGGCTGGGGT	1800
GTGCTCCCTG	ACCAATGACA	GAGGCTGAAA	ATGCCCTGTG	AGCCAAATGGC	AGCTCTCTCT	1860
GGACTCCCTC	GGGCAATGA	TGTTGGCTGT	AATACCTTTT	GTCTCTCTCT	TATGCTGCTC	1920
CATTGCAGAG	AAGGGGACTG	GGACCAAAAG	GGTGGGGAAT	ATGGGAGGCC	CCATTGCTGG	1980
						2040

CCTTGCACT GAATAGGCT ACCCTACCA TTTATTCACT AATACATTTT ATTGTGTTG 2100
 TCTAATTTAA AATTACCTTT TCATCTTGCT TGATTTTCCT TCAGCTAAAT TAGAAATTTG 2160
 TAGTTTTTCC CCTAAAAAT TCAATTGGCAT TTCTTCTTAT AAATITACATT CTCTGATTTT 2220
 CTYTGCAAGC TGCTTCAAGG AAATCATGTT GTTCAAAATG CTGCTCGCA CTCTGCTCCA 2280
 TACCAAAATG TTGCTTAAAC CAATATGTG ACACGAAT TGAGCTGATC GTTCTGGAGA 2340
 AAGTAGCTTT GAACACCA GACCACTGGG TAGTGAAGA GAAGACACCA CATCTGAAC 2400
 TCCCAGTCT GGTGTGAAGG GAGGACAGCT GATAACTGGA TATGAGTGT TCCAGACAT 2460
 CACTGGTCCC AAACATTAC TTCTGCCTGG CACTGCCACA AATACAGTAG GAATGCCATC 2520
 CCCCTTATC TCAGCTTTAA TCCTCAGAGT TTCACTGCTG CTTTATAGCC GAGATGTTAC 2580
 TCGAAGTTCA CATGGAATGC CAAAATTTCC ACAGGCCCTC TTGATTTTTT CACAGTGACC 2640
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 CAATCTACT CTCTCTGCAA CCCACTCAAA GTTTTTTCTT ACCAATTGGA GCCCTTCAGG 2760
 AGTACTTCT TTGAGGTCCC GATAAGACGT TTGTGCTTTC TGTGTGCTTC GATCTCCTGA 2820
 TGCCAGAGT CTTCAAGAT CATTTGCAAT AATCATGACA GAACCAATTT CTTTGTGTGT 2880
 TACATCAACA CAAATTTCAA TCTCTATATC AACCACTGA CAATCTGGGG GCAACCAAGA 2940
 TTTTCCAGT ATTTCAATA TAGCCTGTGT AGSCATCTGT GCCGAATTTA AAAAGCTT 2998

(2) INFORMATION FOR SEQ ID NO:5:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 4152 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Genomic DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

AAGCTTTTTG TGAAAACCT AGGATATGTC CCTCCCTCA CCACACCCAA CCCCCGCC 60
 CTGCCCCAGG ACATAGCAT GCCTCACACA CACACACACA CACACATACA CACAAGCCG 120
 TGAGCTGCAC GCAGGAACAT GGGCTGCATC CACGACACCA TTGAAAAAAT ATACATTATA 180
 TATGTACACC CGGGGCCCCC ACCTGCTCTC CCGTCCCGCC AGCTGGGCCA CACCAAGTCA 240
 CGSAGAGGGG CCGCGGCTG CAGGACCTCA GCACTGCAAG GCGAGGAAGG GAACAGGAG 300
 AAGAAAGGAA GGAAGTTGGA AGGAGGGAG AAATGGGGTC CCGCACTGAA AATGGAATG 360
 AGGTGGGGCG ATCATAGAG AGGACGGAC GATGGTCCAG CTGAGGAGGC CCGCAAGAG 420
 GGGAAAGAGT TCCCATGAC AGGAGAGAGA AGGGAAGGGG AGAGGAGAGG GTTTCCTTCA 480
 ATCCGACCCC CAGCCCCAGC CCCAGCCCCA GCCATTGCAA TCCTGACCTC CTCCCACAA 540
 CAGCAGTGTC TAAGGGGGCA GCTGCCATTG GGGGTAGAAA GGCAGCTGAA GTCCAGCCCA 600
 CTTTCAAACC CAGCCAGCCC CAGTGCAGAG GGCACACCAG GAGCATGACA GCCCAGAAAG 660
 GAGGAGTGGG GGGCCGGGGG AGGGGCAAGG CGGACTCCAG AGGCGCCCTG GGGTTTGA 720
 AATGAAGAGA GGAAGTGTTT TGAAGCTCTT CTCCCTCTTG GTCTCTGTGT TCCGAGAAAG 780
 TCTTCTCCC ATGCTCGAAG TGTCTGTTTC ACCAGGGCAG AATTCGCCCT CTGCGTGGGG 840
 AGAGGTGTAG GCCTTAGTAG CCGTGTGGGG GGGTCTCGAT GATGCGCTCT TCGTCTGCTG 900
 TGGGGGAATC GGGCACCTCC GAGTCACTGC TGTCTCATC CTCTCTGTGG CCCCCAACAG 960
 CCCCGCTCAC ACAGGACTGC CGATTCTGTT AGGACTCCAT GGGGTTCA CA ATGATGTTGA 1020
 GAGCTGAGTC ATCCCAAGAG AGGTCTGGGT CTTTGGGGTC ACTGAGAGCC CCGTGAAGGCC 1080
 CGCCGGCCCC TGAGACCGGG CGGTGAAGGG AATGATGCG CACCAGGCCG AGGACGACCA 1140
 TGAGACCCAG GAAGCCCAAG CACACACAAA TATAGAGGTT TGGCCGCTGT GGTATCATGG 1200
 AGTTTCTGTG GAGAGTGGCT AGCTGTGTCT CAGCATCTC AGGCGGGGGG TGTGACCAC 1260
 GGTGCAGBAA CTGCTGGGAG CTGAGCACGT GCGTGGGGTG GCGCAACCCG TTACTGCTGT 1320
 CAGGACATT GACCTCCAGC ATGAATTACT TGCTGAGTA AGCGCACTTC ATTTCCGAGC 1380
 AGGAAAGCGG GAATCTCTGT GTGTAGAGGG CAGCTCCGTG TCGCAGCCGA TAACGAGCTT 1440
 GCCTCAGGAT CTCTTCATAC ACAGTGTATG TCTCCACCCC AGCAATAGTG AGGTAGGCAG 1500
 ATGTGTGGT GAGCTCCAGC CCGCGCTGCT GAGAGAGGTT TGTGTCCAG AGCAGGCTTT 1560
 CCGCGTCGGG ATCCAGGTCA TCCCCACCA GAGAAATTC ACAGCATCC AGGTTGTGCA 1620
 CAATCTCATC CGACATGCGT GTGTCTGTGA CTGTGCCCTG CCAAGCTTCA TCTTTTGG 1680
 CTTCCACCTG GTGAGAAATG GAGCAGGTGA CTGTGAGATC AGGACATCT GGTATCATGG 1740
 TGTTCCTCT AAGTCCACA GCTGGGGGCG CAAAATGAGC ATGCGCATC AGCAGATCT 1800
 GGGGGGCTC ASGCTGAAG ACAGCACAGT AGCCCTCCAC TACGGGATG GAGACGACAG 1860
 ACTCTTCBCT GAAGCACTTG ACAGCAGTGG TGAGGGGCGAG GGGCTCTGAC CCGGGCGTGG 1920
 CAAAGCGCAG AGTGTTCATG TAAGCCACAT GCTCGAGGGC ATGTTGAAAG GTCTCCACAT 1980
 CATCCCCCTC CAGGGTGAGC AGGGAGCTGT AGGGGTTTCA GTGAGCTTCA ATGCTTTTGC 2040
 CAGAGGCTCT GAAATCCCTA TAGTCCAGCC CTTCCGACCA TGCATAGAGG CACTGATGA 2100
 CCGTCCGGCT CTCCAGGCGA CCTGAGGCGA CCGCTGAACC AGGCAGTAGT CCAATGAAAT 2160
 AGGTTGGAT GACAAAAGAG TCTCCTTGGG TGGTGTCTGT ACTGTGTCTT CCTTTTCT 2220
 TCTCTTGTGT CTCTCTCTCA GTCCAGAGG CCCCATTACT GAGACAGGGC TCCCTCTGGG 2280
 GTGGTGGAT GAGGCCATT TCAATGATGA GGGCAGGCTC GAAGGAGATG CCGTGGGTAT 2340
 AAGGTTGAC TGTGGGAAC TCGAGGTTCA GAGCGTAGTG TACCACTACA CACTCACAGA 2400
 CCGTCTCCAG CTTCAGAGG AACTTGAAGT GCGGGGCAC TCAAGCAGG GGGCAGTGA 2460
 GGAAGGCAAT CCTACAGCGC TGGACAGTCA CGAGATGATG AGAGAGCCCG TCTCAATTCT 2520
 GGCACAGTGT ACATACGATG GTTTCCTCT CTCTCTTGGC CTGTGTGGGA GTTAGGCAT 2580
 GCTTCACTCA GAAGGACAGG GTGAAGTGGT CACTGAGGCT GTCTGTGGGC CAGAGGCCCA 2640

GCCCACTGGG	GCCACCCAGG	GGCACTTGCA	CAGCTGGGT	GCCATTGAAC	CAGTAGATCA	2700
GCGCTGCTGT	CTGGCTGTAG	TGCACCGAGA	GTCCTGCTGT	GCAGTTGGCA	TTGGGCCCAG	2760
GCATGGGCAA	CAGATCCACT	TCCCGAGTGG	CAGCACCA	GAGTTTCCGC	AGCGCCCGCT	2820
CTGAGTAGTT	GTCAACGGTCA	CAGCCCTTGG	CCACATGGCT	GGTCTGCAGC	TCTATTGGTG	2880
CTCGAATGTT	CCAGAGTGGT	TCATCCACAG	TCTCAGGCG	GATACAGGG	AACAAGGCCA	2940
AGCTCCCGAC	ACCTGGTGCA	TATTCTGATC	TTTTGTCCA	GCGTTGCCAG	CTGGGTTTAC	3000
AGGTGGGCTT	CACCTGAATC	TCCACTCTAG	CATCATCTGC	TGCCCGCTTC	TTCCCAAGAT	3060
CATAGCTGCT	CAGCTGAATC	TTATAGAGCC	TCTCAGCAT	GTACTGCAGC	TTCTCTGTGT	3120
TCTCATGTT	CCGCTCATG	TCATAGAGG	AGGCGGTGTT	GGGTGTGAGA	ATCTCATAGT	3180
AGCAGATCTG	GCTGTACTGG	GGGAGCAGAT	CACCTCAAT	GGCTTCCACC	CGCAGATGCG	3240
GATCGTACAG	CTTCCCTCTC	GTCAACGCCG	CAGCATACAG	CCGTTCCACA	AACATCTGGG	3300
CAAACTCGTT	CACATCGTTG	ACCGGCACAT	GCACAGTGGC	CTTGTGGGAC	TTCTTGGTGT	3360
TGGCCCGCTG	GGGGCCCTCG	CCACAGTCAT	AGGCTGGAT	GGTGAAGTGT	TGTTCTCTCT	3420
GGGCGCTCGA	GTCACAGGCG	TCTTTGGCCG	GATCAGCCG	CTCTCGCTTG	GCCTTGTCAA	3480
GGATCAGACG	CTCAAAGGCG	ACCCGACAGC	CATGGAGCCG	GAAAGCCGAG	ATCTCACCTG	3540
CATAGCGCAG	CGGGGATCCG	TTGTCCAAGG	CAAGAGTGGG	TGGATTCACT	AGGACCGTGT	3600
TGTCATCTCT	CATGACGATG	CCCTGGTACT	CTGCTCAAT	CCATGGCTTG	TGCTTGTGGG	3660
CTTTGTGACA	GGAGCAGGAG	GGCAGCAGAG	AGGCGAGCAG	AGGGGCGAG	ACGAGAGGGG	3720
TGATGCTGCG	GCTGGGGCA	GGGACAGGCG	AGGCGTTTGC	CTCCCTGGGG	AGCCTCACGC	3780
CTGCGGATTC	CACCTTGGCG	GAGGAGATACA	GGGGGGGAAA	ACCAAAATAA	AACGTCAAT	3840
AAATTGTGTA	GAGGAGGTCC	AGCTTATGAG	CGGGCCAGAG	CCAGGCGAGG	CTCGGGGAGG	3900
GGGCGCTCTG	AGGTTACAGG	GATCATGCTG	GCACACCGCG	CCACCCCTGG	AGCCAGTTAT	3960
TTTGGCATGG	CTTGATTGCG	AACAGCTGCC	TCTCTGTGTA	TGGCAGACAG	CACCGTATC	4020
AGGATCTCTT	CTCCACAGTC	GTACTTCTGC	TCAATCTCTC	TGGCAAGTGT	TCCCTCAGGG	4080
AGCAGAGGTT	CTCTCGTATG	CTCCCGCTG	TCTGTGAGCA	GTGATAGGTA	CCCATCTCTG	4140
ATCTTTGGAT	CC					4152

(2) INFORMATION FOR SEQ ID NO:6:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 3117 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Genomic DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

GGATCCAAAG	ATTGCGCAGC	AGTGCCACCA	TCATGAACCT	CCAGGCCAGC	CCCAAGGGTC	60
AGAACACAGC	GAAGCGTTGC	CTCTTTGGGG	GCCAGGAACC	AGCTTCCAGG	GAGCAGCCCC	120
CTCCCTTGCA	GCGCCCCAG	CAGTCTCTCA	GAGTGAAGGA	GGAGCAGTAC	CTGGGGCAGC	180
AGGGCTCAGG	AGGGGCACTG	TCCACTCTCT	AGCCTGTGGA	ACTTGGCCCT	CTCAGCAGCC	240
TGGCCCTGCT	GAACCTGTGT	GTGTATGGGG	CTGAGCGGAC	CTCAGCAGCC	ATGCTGTCCC	300
AGCAGGTGGC	CTCAGTAAAG	TGGGCCAACT	CTGTGATGGC	TCCAGGGCGG	GGCCCGGAGC	360
GTGGAGGAGG	TGGGGGTGTG	AGTGACACGA	GCTGGCAGCA	GCAGCCAGGG	CAGCCTCCAC	420
CCATTTCAAC	ATGGAACCTG	CACAGCTCTG	CCCTCTACAG	TGCAACCAAG	GGGAGCCCGC	480
ATTCTGGAGT	GGGAGTCCCG	ACTTACTATA	ACCACCTCTG	GGCACTGAAG	CGGGAGAAAG	540
CGGGGGCCCC	ACAGCTGGAC	CGCTATGTGC	GACCAATGAT	CCGACAGAGG	GTGAGCTGG	600
AGGTAGGGGG	GCCCGAGCA	CCCTCTGAAT	CTTTCACAG	AGCCACAGAA	CCGCCAAGCC	660
AGTCACTGCG	CCCTGCAACC	TTCCAGCTGG	CATTGCGCCA	CAGGTTGAAC	CGGAGGCTCT	720
TCGCGCAGGG	CCACCGCCCC	CCAAACCCGG	TGGCTGCCCT	CCCTTCCACG	AAGCAGCAGC	780
AGCAGCAGCA	ACCACAGCAG	CAGCAGCAGC	AGCAGCAGGG	AGCCCTACCC	CAGATGCCCG	840
CTTTTGAGAA	CTTCTATTCC	ATGGCCACAG	AACCTCTGCA	GCACCCAGG	GACTTTGGCC	900
TGACGCGCAG	TGGGCCACTG	GGAGCACTCC	ACCTGGCTCA	CCACAGCATG	GCACCTTACC	960
CCCTCCCCCC	CAACCCAGAT	ATGAACCCAG	AACTGCGCAA	GGCCTCTCTG	CAGGACTCAG	1020
CCCCGAGGCC	AGGCGTACCT	CAGGCTCAGA	TCCCTTCTCC	CGCGCGCTCT	CCTGCGCTCT	1080
CTAAGAGGGG	TATCTGCTCT	CCGAGGCCCG	TGGATTGGGG	TGGCACCGAG	CTGGGCGAGG	1140
AGGCACTGCG	CAGCTTGTTC	CTACATCACT	GGCCCTTGCA	GCAGCCGCGA	CTGGCTTCC	1200
TGGGCGAGCC	CCATCTTGAA	GCTCTGGGAT	TCCCGCTGGA	GCTGAGGAGG	TGCGAGCTAC	1260
TGCTCTGATG	GGAGAGACTA	GCACCCAAAT	GCCGGGAGCG	AGAGGCTCCT	GCCATTGGCA	1320
GCAGGAGGCG	CATGAGGGCA	GTGAGACAG	GGGACTGTGG	GCAGGCTGTA	CGGGCGGGAG	1380
TGATCTCAGG	CAGCGCAGCG	AGGCGCCGGG	CATCCAGGGA	GGCCAAATTT	GTGACCTGG	1440
CCAGAGAGGC	TGTGGAGCTG	GCGCTCACTG	AGAAATGCAA	GGATGGCAGT	GGTTCTGAAG	1500
AGAGAGCGAA	AAGTGTATTT	GCTCTCACTA	CCAAGTGTGG	GCTGGATTTT	TCTGAGCTTT	1560
CTTATGACCA	CAGGAGAGCA	CGAGAGAGAT	CTGAGTAGGT	ACCCCTCATC	ATCCGACTGT	1620
CTGTGCTGCT	GCGAAGCTGT	GACCCAACTG	AGGCAAGCCG	GGTGGAGGCT	CTTGATGAGG	1680
ACGGGAAGGG	TCTTGAACAG	AACCTCTGCT	AGCACAAGCC	ATCAGTCATC	GTACCCGCGA	1740
GGCGGTCCAC	CCGAATCCCC	GGGACAGATG	CTCAAGCTCA	GCGGAGGAGC	ATGAATGTCA	1800
AGTTTGGAGG	GGAGCTTCTC	TGCGGGAAGC	CAAAGCAGCG	GCGCCAGGCC	GAGCCCTCAT	1860
TGATCCCGAC	CAAGGCGGGG	ACTTTTATCG	CCGCTCCGCT	CTACTTCAAC	ATCACCCCAT	1920
ACGAGGCCCA	CTGCGCTCTC	CCGCTGGCGC	TAGCTGACCA	CCGCTCTGAG	CGGAGCTTTG	1980
ACCTACTCTC	CTACACGCGG	CCCCCATCC	TACGCGCTGT	GCGGGAAGGC	TCTGGCTCTT	2040

ACTTCAATGC CATCATATCA ACCAGCACCA TCCCTGCCCC TCCTCCCATC AGCCTAAGA 2100
GTGCCCATCG CACGCTGCTC CGAGCTAACA GTGCTGAAGT AACCCCGCCT GTCTCTCTGT 2160
TGATGGGGGA GGGCACCCCA GTGAGCATCG AGCCACGGAT CAACGTGGGC TCCGGGTCC 2220
AGGCAGAAAT CCCCTTGATG AGGAGCCGTG CCTTGGCAGC TGAGATGCC CACAAGGCTC 2280
ACTTGGGTGG GAGGACATGG GAGGACCTAG AGAGCAGCGG GSAGAACGAG AGGCAATGG 2340
AGACCTTGCT GACAGCCGCC TGCTGCACCA TTTTCCCTGG TGCTGGACC AACCAAGAGC 2400
TGCCCTTGCA CTGCTGCAC GAATCCAGAG GAGACATCTT GGAACCGCTG AATAAGCTGC 2460
TCTCGAAGAA GCGCCCTGCG CCCACAACC ATCCGCTGGC AACTTATCAC TACAAGGCT 2520
CTGACCAGTG GAAGATGGCC GAGAGGAAGC TGTTCAACA AGGCATTGCC ATCTACAAGA 2580
AGGATTTCCT CTTGGTGACG AAGCTGATCC AGACCAAGAC CGTGCCGACC TGCSTGAGT 2640
TCTACTACAC CTACAAGAA GAGGTGAAA TCGGCCGCAA TGGGACTCTA ACCTTTGGGG 2700
ATGTGGATAC GAGCATGAG AAGTCGCCCC AGGAAGAGGT TGAAGTGGAT ATTAAGACTT 2760
CCCCAAAGTT CCCAAGGGTG CCTCTTCCCA GAAGAGAGTC CCCAAGTGA GAAGAGGCTG 2820
AGCCCAAGAG GGAGGTGAAG AGGCCCAGGA AGAGGGGGA GGAAGAGGTG CCAAGATCC 2880
AAGAGAAGGA GGAGCAGGAA GAGGGCCGAG AGGCGACGAG GCGGGCAGCG GCAATCAAG 2940
CCACGAGAGC ACTACAGGC AATGAGTCGG CCACTGACAT CCTCATCTCT CGAGGCACG 3000
AHTCCAGCG CCCCTGGCTT GCGGCTGGCC AGGCCTCGGA GAAGCCCAAG GAAGGGACAG 3060
GGAAGTCAGC AAGGCACTA CTTTTTTCAG AAAAAAAAA AAAAAACAA AAGACTT 3117

(2) INFORMATION FOR SEQ ID NO:7:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 3306 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Genomic DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

GAATTCGGCA CGAGGTCAGT TTCTGTGGGA ACACAGAGGC TGCTGTGCC ATTACAGAA 60
CGACGGATAC AGACAGGCTT TGCTCTATAA GGGATCCCA CAGTGGATTT GTTTTAATC 120
TTAATCCGCT AACAGTTCG CAAGGATATA ACGTCTCTGG ACTTGGGAAG ATTTTATGT 180
TTAATGTCTG CGGCAACAATG CCTGTCTGTG GACCACTCT GGGAAACCTG GCTTCTGGCT 240
GTGAGSCAGA AACCCAAACT GAAGAGCTCA AGAATTGGAA GGCAGCAAGC CCAGTCGGA 300
TTGAGAAAGC CCTCCAGCTG TCCACAGAGG GCTTATCAC TCTGACTAC AAAGGGCCTC 360
TCTCTGCCAA AGGTACCGCT GATGCTTTTA TCGTCCGCTT TGTTTGCAAT GATGATGTTT 420
ACTCAGGGCC CCTCAAAATC CTGCATCAAG ATATGACTC TGTGGCAAGG ATCCGAACA 480
CTACTTTGA GTTTGAAACC GCGTTGGCTT GTGTTCTTTC TCAAGTGAGC TGCCAATGCA 540
CCGAGCTGGC TGGAAATGAG TAGCACTGTA CTGGCTAAG CAGAGTCAAG AAACCTTGA 600
CGCGTGTGGA CAGCTGTGTC GATGGAGAGA AGAGGACTTT CTATTGAGC GTTTCGAATC 660
CTCTCCCTTA CATCTCTGGA TGCCAGGGCA GCGCAATGGG GTCTTGCTTA GTGTGAGAAG 720
GCAATAGCTG GAATCTGGT GTGGTGCAGA TGAGTCCCCA AGCCGCGGCG AATGGATCTT 780
TGAGCATCAT GTATGTCAAC GGTGACAAGT TGGGGAACCA GCGCTTCC ACAGGATCA 840
CGTTTGAAGT TGCTCAGATA TCGGGCTCAC CAGCATTTCA GCTTCAGGAT GTTTGTGAGT 900
ACGTGTTTAT CTGGAGAACT GTGGAAAGCT GTCCGTTGT CAGAGTGGAA GGGGCAACT 960
GTGAGGTGAA AGACCCAAGG CATGGCAACT TGTATGACTT GAAGCCCTG GGGCTCAAGC 1020
ACACACTCGT GAGCGTGGC GAATACACTT ATTACTTCGG GGGTCTTGGG AAGCTTCTT 1080
CAGACCTGTG CCCACCAAGT GACAAGTGA AGTGTGCTC CTCATGTGCA GAAAGCGGG 1140
AACCGAGGG ATTTCACAA GTGGCAGTCT TCTGACTCA GAAGTCACT TATGAATAAT 1200
GCTTGTAA AATGAATCTC ACGGGGGGGG ACATTGCCA TAAGGTTTAT CAGCGCTCCA 1260
CAGCACTCTT CTCTACTGT GACCCGGGCA CCGAGCGGCC AGTATTCTA AAGGAGACTT 1320
CAGATTGTTT CTACTTGT TTGAGTGGCA CCGAGATATG CTGGCCACTT TTCAATCTGA 1380
CTGAATGTTT ATTCAAAGAT GGGGCTGCCA ACTCCTTCCA CTTCTGCTC GTGTCAAGT 1440
ACAGTGACAA CTGGGAAGCC ATCACTGGGA CGGGGAGACC GGAGCAGTAC CTCATCAATG 1500
TCTGCAAGTC TCTGGCCCGC GAGGCTGGCA TGAAGCTG TGAGCCGTG ACGCTCAGAA GCAGCGGCT 1560
GTCTGCTGGG TGCTGTCAGC CCGGTGAACC TCGGCAAGGT AACGACAGGA CCTCAGTGA 1620
GAGATGGACT AATTGTCCTG TCGAGGCTG ATGCGACTT ATGTCCAGAT GGGATCGGA 1680
AAAGTCAAC CACATGACA TTCACTTGA CCGAGAGCCA AGTGAATCC AGGCCCATGT 1740
TCATCAGCGC CTGGAGGAGC TGTGATCTA CCTTTGCTG GCGCCAGGCC ACAGCTGTCT 1800
CCATGAAGAG CAACGAGCAT GATGACTGCC AGGTCAACAA CCCAAGACCA GGACACTGT 1860
TTGATCTGAG CTCCTTAAGT GGCAGCGGCG GATTCAAGC TGCTTACAGC GAGAAGGGGT 1920
TGGTTTTACT GAGCATCTGT GGGGGAAGT AAAACTGCC CCTGCGCTG GGGGCTCTGT 1980
TTGGACAGAC CAGGATTAGC GTGGGCAAGC CCAACASAGG GCTGAGATAC GTGGACAGG 2040
TCTCGAGCT GGTGTACAG GATGGGTCCC CTGTGCTCT CAATCGGCG CTGAGTATA 2100
AGAGTGTGAT CAATTGCTGT TCGAGGCTG AGCGCGGCC ACCCAATAG CCCATGCTCA 2160
TCTCCCTGGA CACATGACA TGCATCTCT TCTTCTCCTG GACACGCGC GTGGCTCGG 2220
ACAAGCGAC CCAATGTTCT GTGAGGAATG GAAGCTCTAT TGTGACTTGT TCTCCCTTA 2280
TTCACTCCAC TGGTGGTTAT GAGGCTTATG ATGAGAGTGA GGAATGATCC TCCGATACCA 2340
ACCCTGATT CTACATCAAT ATTTGTGAGC CACTAAATCC CATGACAGGA GTGCCCTGTC 2400
CTGCGGAGAG CGTGTGTGTC AAGTTCCTA TTGATGGTCC CCCCATAGAT ATCGGCGGG 2460
TAGCAGGAGC ACCAATCTC AATCCAATG CAATAGATAT TTACTGAAT TTGGAAGCA 2520

GTACTCCTTG CCAGGAATTC AGTGTAAAT AAAATTGAAC CTGCTCAACA GCTGAGGGAG 2580
 ACTAGAATG ATGGGTCCAT ATCTCGGTGC ATTTGTCAT AATTCACACA ATGGTGCAGC 2640
 TACGACGTG TAATTTTATG GAGCTGCATA CAAGGCTTT TCTTGAAGCT GAACCAAGAA 2700
 CAATCTCTTA TGTTCCTTAG GCTTCTGTA ATGTGCAGGA ATATATGGAT ATCTGAGGAG 2760
 TTCAAATTT GGTCTCCAGC AGTTACCAAT GCAATCGTCA ATGACCCAGT CTTCGAAACG 2820
 TCCATCTCTGA GCACCCAGTA TCTCTGTCAAT TAAGCGTTTT AGTCCTTCAA CTTCATCTTC 2880
 TCTCGGGTGA AGTTCACCAC CAGGTAGTTT GAAGAAGTT GTTCCCAGCT GCAGCAGTAA 2940
 CACATCGGGT AGCGGGTGC CATGTACAAT CAGAACCCCT CTACAGTCC TCCTCATTCC 3000
 AATTTTATCA AATCTCTCCC TCATCGCGTG AAATCTGGCT GCAACAGAGC TGCTCTTCTC 3060
 GTAGAGGGGC TCTTTTGTAC CAAAGATATA ATTGTAGA GGGTACAGT TGA7GGTGGC 3120
 CTCGAGGGTG AGGGGCTTCG TCTGCTGGAT GTACTTGTGT CGAAGCTGAG TGACCCCCCG 3180
 GGCGCCAGCG GTCTCGAGC GATTGGCGCG TACCACAGAC ATGCTGGGGA GCTCCGGCGC 3240
 TGACGCGGAG CAGAAAGTGG CAGGCAAGGT AGACTTTCCG CGTCCGGGAA GCTCTGTGCC 3300
 GAATTC 3306

(2) INFORMATION FOR SEQ ID NO:8:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 4218 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Genomic DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

GAATTCGGCA CGAGAATGGA TCAACCTCAA CACACGTTA AAGTAGAGC AAAGAAGTAA 60
 TACACAGTGT ATGAGTCTCA CATGAAATAC CCGAGTGTA ATCCAAGAA ACAGGAAGCA 120
 GATTGGTGGT TGGCAGGAGC AAGGGCGGTG GAGGAGGAAA ATGGAAGATA ACGGAGCTTT 180
 ACTTTTGGAG TGATGAGAAAT GTTTTGGAGC TAGATAGAAG TGTGTGTTGT ACACATTGT 240
 GGATGTACTA CCACTTAATT GTTCACTAA AAGATTAAT TATGTGAATT GCATCTTAAT 300
 TAAACAAG GATAACATTC CAACTCTGG ACATATCCT TCTTTCCAT TTGATGTGAG 360
 GCGCCTGTGA GAATTCATCAT CCGGTTTGGT CACTGCACCT AAGATGTGGA GAAATTAGGA 420
 CGCACAGTTA AGAGGAAGGA TAACACTGAT TAAGGTAGTG CTTTTTCAGG TTTCCCTTAA 480
 ACAATTTAAC AGATGGATAG TGGCACCACT TACGAGATGG AAAACACAGC GGAAGGAAGA 540
 TTTGGGGGAG AAGTTAAGTT TGTCTTGGCG CTGTGTTTT CAACTTGAGT GTAAAGAGCA 600
 TATGTTAAGT CTTCAGTGGC GAAACACTAA AACTAGAAAT GGAATCAGAA TTTATCTTTG 660
 AATCTTGACT CTCGAAGATG GTCTTGTGAC TTCAGTGCCCT GGTCAAATGA CAGATGTGGC 720
 AATCTTTTCC TGAAGGTCCA AGCACTGAA CGTGGCAGGG TGACCCGAT CCGATTTGCT 780
 CTCAATTTGT GCAATAAAT CTGCAACGTG ATGGCGGAC TCTCGCGGCC CGAGCGGCGC 840
 GACCTTGTCT TCGAGGAAGA GGACCTCCCC TATGAGGAGG AAATCATGCG GAACCAATTC 900
 TACTTCAAAAT GCTGGCTTCA CTACATCGAG TTCAAACAGG GCGCCCCGAA GCCCAGCGCTC 1020
 AATCAGCTAT ACAGAGCGGGC ACTCAAGCTG CTGCCCTGCA GCTCAAACT CTGGTACCGA 1080
 TACCTGAAGG CGCGTCGGGC ACAGGTGAAG CATCGCTGTG TGACCCGACC TGCCATGAA 1140
 GTATGTCAACA ACTGTCACTA GAGGGCCTTT GTGTTGATG ACAAGATGCC TGTCTGTGG 1200
 CATGATTACT GCGAGTTCCT CATGAGGACG GGGCGCTAGA CACAGACGCG GCGCACTCTC 1260
 GACCTGCCCT TCGCGGCACT GCGCATCAGC CAGCACTCTC AAGTTGGCC CTTGTATCTG 1320
 CGCTCTCTCG GCTCACACCC ACTGCTGAG ACAGCTGTGC GAGGCTATCG GCGCTTCCTC 1380
 AAGCTGAGTC CTGAGAGTGC AGAGGAGTAC ATTGAGTACC TCAAGTCAAG TGACCGGCTG 1440
 GATGAGGCCG CCCAGCGGCT GCGCCACGTG GTGAACGACG AGCGTTTCGT GTCTAAGGCC 1500
 GGCAAGTCCA ACTACCAAGT GTGGCACAGC CTGTGCGACC TCATCTCCCA GAATCCGGAC 1560
 AAGGTACAGT CCTCAATGT GGACGCCACT ATCCGCGGGG GCGTCAACCC CTTCACCGAG 1620
 CAGCTGGGCA AGCTCTGGTG TTTCTCGGCC GACTACTACA TCCGACGGCG CCAITTCGAG 1680
 AAGGCTCGGG ACCTGTACGA GGAGGCCATC CGGACAGTGA TAAGCTGTGG GGAATTCACA 1740
 CAGGTGTTTG ACAGCTACG CATGTGCGAG GAGACAGTGA TCTGCTCAA GATGAGTACA 1800
 GCTCTGAGG TGGGCGCGGA GGAAGAGGAT GATGTGACAC TGAGGCTGCG CTTGGCCGCTC 1860
 TTTGAGCAGC TCATCAGGCC GCGGCCCTGT CTCTCAACA GGTCTTCTGT GCGCCAAAAC 1920
 CCACACACAG TGACAGAGTG GCACAAGGCT GTGCGCTGCG ACCAGGGCCG CCCCGGGGAG 1980
 ATCATCAACA CCTACACAGA GGTGTGACAG ACGGTGGACC CTTCAAGCG CACAGGCAAG 2040
 CCCCACACTC TGTGGGTGGC GTTTCGCAAG TTTTATGAGG ACAACGGACA GCTGGACGAT 2100
 CGCCTGTGTA CTCTGGAGAA GCGCCACCAAG GTGAATCTCA AGCAGGTGGA TGACCTGGCA 2160
 AGCGTGTGGT GTCAGTGCGG AGAGCTGGAG CTCCGACAGC AGAATCTAGA TAGAGCTCTC 2220
 CCGCTGCTGC GAAAGGCCAC GGCCTGTGCT GCGCCGCGGG CCGAGTACTT TATGTTGTTA 2280
 GAGCCGCTGC AGAAGCGGCT GTACAAAGTCA CTGAAGGTCT GGTTCCTGCT GCGCAGCTG 2340
 GAGGAGGCC TCGGCACCTT CCACTCACCC AAGGCCGTGT AGCAGCGCAT CTGGAGCTG 2400
 CGTATCGCAA CACCCAGAT CTGATCAAC TATGCCATGT TCTCGAGGGA GCACAAGTAC 2460
 TTTGAGGAGA GCTTCAAGGC GTACGAGGCG GGCACTCGC GTTCAAGTG GCCCAAGCTG 2520
 TCGGACATCT GGAGCACTTA CTTGACAAA TTCAATGGCC GCTATGGGGG CCGAAGAGCTG 2580
 CAGGCGGACG GGAAGCTGTT TGAACAGGCT CTGGACGGCT GCGCCCCAAA ATATGCCAAG 2640
 ACCTTGATCC TGTGTTACGC ACAGCTGGAG GAGGAGTGGG GCGTGGCGCC GCATGCCATC 2700
 GCGCTGTAGC AGCGTGCCAC CAGGCGCGTG GAGCCCGCC AGCAGTAGTA CATGTTCAAC 2760

ATCTACATCA AGCGGGCGCG CGAGATCTAT GGGGTACCC ACACCCGGCG CATCTACCAG 2820
 AAGGCGATTG AGGTGCTGTG GGCAGGACAC GCGCTGAGA TGTGCTGCG GTTTCAGAC 2880
 ATGAGGTGCA AGCTCGGGGA GATTGACCG GCGCGGGCCA TCTACAGCTT CTGCTCCAG 2940
 ATCTGTGACC CCGGACACAC CGGCGCTTC TGCGAGACGT GGAAGAGCTT TGAAGTCCCG 3000
 TACACACCG AGGTCAACTT CATGGCTCG CAGATGCTCA AGGTCTCGGG CAGTGCCACG 3060
 GGCACCTGTG CTGACTGGC CCGTGGGACG AGTGGCATGG AGCAGATGAA GCTGCTGGAA 3120
 CAGCGGGCAG AGCACTGGC GGCTGAGGCG GAGCTGACC AGCCCTTGGC GCGCCAGAGC 3180
 AAGATCTGTT TCGTGAGGAG TGACGCTCC CCGGAGGAGC TGCGAGAGCT GGCACGACAG 3240
 GTCAACCCCG AGGAGATCCA GCTGGCGAG GACGAGGAGC AGGACGAGAT GGACCTGGAG 3300
 CCCACGAGG TTGCGCTGGA GCAGCAGAGC GTGCCAGCG CAGTGTTTGG GAGCCTGAAG 3360
 GAAGACTGAC CGTCCCTCT GTGCCGAAT CGGCACGAGC AAGACAGGCC CCGAGATCAT 3420
 TTGCGTCAAA GGTTTTCCTT CGAGATGACA AATGTTTCAA GGAATCTCAA ATTTTACAAA 3480
 GTTTGAAGTG TGCGATTGG TGCGCTGGG CTGTGCTCT TCTGTGAGC TGTTTCTCC 3540
 CTACATCCCT GAAAGGAAGT TGAGCTGCT CTGCTATCG CAGACCTCCC TTCCAGCGCG 3600
 CCAAGGATG GGTGTGCTG AGGCGAGCAT GCTAGTGCTG ACCGTGCTCC TGCGCTCCAG 3660
 GCGCGTGCTC CTCTGTCTC TAGCCCACTA AGGCCCTGGC CCATTTTGTC TAAACAGGCA 3720
 GTCGAGCTA GAAAGAGCAG ACAATCTCT TGCGTACCA GTCTGGCTAG GAGCTGTGCT 3780
 CCTGACTGGG ATCCAGGCTT TCTCCCTCG CCATGTGAAT TCCAGGGGCG AGAGCTGAA 3840
 ATGTTGAACA CAGCACTGGC CAAAGAGATG TCACCGTGGG AAGCAGGCT CTCTTCTCT 3900
 CCTGCTGCT TTGCTGGGT CAGAGTAGCT GAGGCTGTCT TGAGAGAGT TGGAGTGCTG 4020
 GTTTTCAACC TGGTGGTGT GCTTTGCTT GAGGGCACTT AGAAGGCCA GCCAGGCTCT 4080
 TGTCTCTGCC CTGACACAG CGAGCGGACT TTCTAGGTA TGCTCTGAT TTCTGAGAA 4140
 CGCAGGAGTG GATGAGGACC AAGAGGAAG GTGACTGAA CTGTCCACTC ATAGCCCGCG 4200
 TGCGTATTG AGAGGGCT

(2) INFORMATION FOR SEQ ID NO:9:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1187 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Genomic DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

GAGCTCGCG GCCTGAGGT CGACACTAGT GGATCCAAAG AATTCCGGAC GAGGAAACT 60
 CAACGGTGTG CGAGTGAAGG ACAGGAGACG AGCCTCTGT GGTGGAGCA CCCACCTCG 120
 AGGAGCTTCC TGAGCAGGTG GCAGAGATG CGATTGACT GGGCGACTTT GGGGTAGAGG 180
 CAGTGTCTGA GGGGACTGAC TCTGCACTCT CTGCCGAGCG TCGTGAATC GACTGGGGCA 240
 TCTTCCCGGA ATCAGATTCA AAGGACTCTG GAGGTGATGG GATAGACTGG GGAGACGATG 300
 CTGTTGCTTT GCAGATCACA GTGCTGGAAG CAGGAACCCA GGCTCCAGAA GGTGTTGCCA 360
 GGGGCGCAGA TGCCCTGACA CTGCTGAAT ACATGAGAG CCGGAATCAG TTCTT GATG 420
 AGCTCATGGA GCTTGAGATC TTCTTAGCCC AGAGAGCAGT GGAATTGAGT GAGGAGCGAG 480
 ATGTCTGTCT TGTAAGCCAG TTCCAAGCTG CTCACGCCAT CTTGAGGGC CAGACCAAG 540
 AAGAGAGTGT TACCATGGTG TCAGTGTCTG AGGATCTGAT TGCGCAGGTT ACCAGTCTC 600
 AGCTGCAACA CCTGTTTATG ATCTGGCTCT CACCAAGSTA TGTGGACCGA GTGACTGAAT 660
 TGAGACGCA GAGGACACTT GAGGAGCAGG CGGCTCTGGA GCCTAAGCTG GACCTGCTAC 720
 TGAGAAGAC CAAGGAGCTG CAGAAGCTGA TTGAAGCTGA CATCTCCAAG AGGTACAGCG 780
 GGGCGCCTGT GAACCTGATG GGAACCTCTC TGTGACACCC TCGGTGTTCT TGCTGCCCA 840
 TCTTCTCCCG TTTTGGGATG AAGATGATAG CCAAGGCTGT TGTTTTGGGG CCTTCAAGG 900
 CAAAGAGCCA GGCTGACTGG AAGATGAA A GGCACAGGAA GGAAGCGCA CTTGATGGTG 960
 ATCTTGGCAC TCTCATGTT CTCTACAAGA AGCTGTGGTG ATTTGCGCTG TGGTCTATCA 1020
 GGGCAAAACC ACAGATTCTC CTCTAGTTA GTATAGCGCA AAGAGCTTCT CGAGAGTACT 1080
 TCTAGAGCGG CCGCGGGCCC ATCAGTTTTC CACCGGGTG GGGTACC 1187

(2) INFORMATION FOR SEQ ID NO:10:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 3306 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Genomic DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

CCCTCACTAA AGGGAACAAA AGCTGAGCT CGCGCGCTG CAGGTGCACA CTAGTGGATC 60
 GAAAGTTCGT TACGCCAAGC TCGAATATTA CTCTGGGCTG ACCATAAAT ATTGTGCTGA 120

TCTAGGATAT AGTTGGTTT CTTCGGGCA GCAATCTGGA TGAGGCGGTT GAGGCACTGG 180
 GTGGCGCTGT GGATCAGGAC ATCCCAAGCG CCAGCATAGT TCGGCTGCGG CGGTAGGCCCC 240
 ATCACCAGCA TCTTATCCAT GATGGCATTG GTACCCAGGA TTGTGTACTT CTTGAAGGG 300
 TTGGAGGCTG CATGTTTGAT GGCCCATGTG GTCTTGCCAG CAGCAGCGAG GCCCACCATC 360
 ATCAGAATCT CACATTCTGC CTGTCTCTTT GGTCCAAAGG TGCCCGGATG ACGTCACTA 420
 AGGGGAAGGT GCTGGATGAA GGTAATACCC GGGAGAGCAG AACATAGGG CTCTGCTCTC 480
 TGTCCBAAGT TGAATCCAC TGGCAATTTC TTCAACAGGA CATGAGGATA GAGGGCTGGA 540
 CCCCCAAGG CTTCCTGTG GATTCCGAAA GCAATGGCCA TCCACTTTC ATTCTTGTA 600
 AAGACAGAT CCAGGTGATT TCCACATCA AATCCGAA AGACCAAT CACCGAGAG 660
 CTCTCGGGTG CTAGGAGAGC GGTGGGCCCT GCAGACTGGG GGGAAAGCTC CGACAGCCCA 720
 GTGGGCCCCA GGATCAGGCC CCGCTGGGCC TGGAGAAGCC CAGTCTGGGC TGGAGCGGGA 780
 GCTGGACAGT GTGGCCTTGC GTTCGCCCCC GGGAGCGCTC CAGTGTGCG GGCTCGGGT 840
 GGAATTTGCT AGCACCAATA CTTCAAGGTT GCCAACCTGG GGTTTTAGCT CCCTTGGTTT 900
 TAACTCCCTA GGGCGGGTG GGGGACAGGG AGGAAGGATG GGGCAGCTGG GTGCAATCCT 960
 GCTGAAGCC AGCCATTCTT TGAATTTCTA GAATTAAC TAACGCTGCGC CGGAGGCCG 1020
 CGGGGGCCGG AGCGAGCAG CCGCGGCTGA GGTTCGCGAG TGCGCGCTC GGGGCTGGC 1080
 TCGGCGCGG GGACCCGGG CTCTGGCCGC GCGCGCTCCG GCTTCGGGG GGGCGGGG 1140
 CGCGGAGCA TGGTGCAGT CGCACCGCTT CCGCGCGGCC GGTGAGTGG CGGCGGGG 1200
 CCGGCTGGG ACCTCCGAG GGAAGATGT TTTCCGCCCT GAAGAAGCTG GTGGGTGGG 1260
 ACCAGGCCCC GGGCGGGAG AAGAATCAT CTGCGGGGCT CAGTCCATG AACCGGCT 1320
 TCGCAGAGCG CTTCGCCAAG GGGTGCAGT ACAACATGAA GATAGTGAT CGGGAGAGCA 1380
 GGAAACAGCG CAGACAGCGC CTGTGGCCACT GCGTGCAGGG CCGGCGCTG GTGAGGAGT 1440
 ACATCCCCAC ACAGAGATC CAGGTACCA GCATCCACTG GAGTACAAG ACCACGATG 1500
 ACATCTGAAA GTTGAAGTC TGGGATGTAG TAGACAAAGG AAGATGCAAA AACCGAGGCG 1560
 AGCGCTTAAA GATGAGAAC GACCCGAGG AGNCGAGTCT TGAATGGCC TTGATGCTG 1620
 AGTTCTGGA CGTATCAAG AACTGCAGC GGGTGTGAT GATGTTGAG ATTACAGC 1680
 AGTGAACCTT CAATTACAT CTCCGGAGC TTCCAAAAGT GCCCACCCAC GTCCAGTGT 1740
 GCGTGTGGG GAACATCCGG GACATGGGC AGCACCGAGT CATCTGGCG GACGAGTGC 1800
 GTGACTTCAT CGACACCTG GACAGACCTC CAGGTTCCTC TACTTCCGC TATGCTGAGT 1860
 TCTTCATGAA GAACAGCTTC GGCCTAAGT ACCTTCATA GTTCTTCAAT ATCCATTTT 1920
 TCGACCTTCA GAGGAGACG CTGTTGCGGC AGCTGAGAG CAACACAGTG GACATGAGC 1980
 CACGCTGGA GGAAGTGTG GTGACAGCAG AGACGGAGGA CAGAAGTAC GGCATCTTCC 2040
 TGGAGATGAT GAGAGCTCG AGCCGTGGCC ATGCTTCCC ACTGGCGGCC AACGGCAGA 2100
 GCCATCCG GGGTCCAG TACTCAGTC TGCTTGACG CCGTGTGTC ACAGGAGCT 2160
 CCAGCCCGGG CACAGCCAG CCGGCCAC AGCTGCCCTT CAATGCTGC CCACATCTCT 2220
 CTGTGCCCC TGTAACACC TCAGAGGCC TGCCGCCACC TCGTGGCCC TCAGGCCCGC 2280
 CCCCAGCGCG CAGCATATC TCTAGGCTGT TTGGAGCTC ACTCTCCACC GAGGACGCC 2340
 CTCACCTCC AGAGCAGTC CCGGCCGAC AGGGCCGAGC AACGCTCAG AGTGTGAGG 2400
 ACTTTGTCC TGACAGCCG CTGAGCCGCA GCTTCTGGA AGACACAAC CCGCCAGGG 2460
 ACGAGAAGAA GGTGGGGGCC AAGGCTGCC AGCAGACAG TGACATGAT GGGGAGGCC 2520
 TGGCGGCAA CCGATGTTG CGAGGGTTC AGACAGATG GGACTTCGA GACCAGCAC 2580
 GTGGAGTCC CCGCTGCTC CGAGGCCCG TCCGAGTCA AGACATGCT CTTTGAAGT 2640
 AGGAGAACG AGAATGGCA GCTCCACAA AAGGCGCTG CCGAGCTCC CAGCATGCT 2700
 CAGAGCCAGA GACCAAGTG TCTCATAC CAGCTTCGAA GCGACCGAG GGGACAGCTC 2760
 CCACGAGGAC CGACAGACC CCTTGGCCAG GGGGTGCTC TGTTCGACA GGTCCGAGA 2820
 AGCGCAGCAG CACCAAGGCC CTGCTGAGA TGGAGCGGG GAAGGCTGAG CAGGCTCCT 2880
 GCTCGAGAG TGACCCCGAG GGAACCATG CTGCAAAAT GCTGTCTTC GTATGGATG 2940
 ACCCGACTT TGAGCGGAG GGAATCAGCA CACAGGCGAG GCGGATAG TTCCGCTGC 3000
 GAGATGACC CTCCGATGTG ACTGACGAG ATGAGGGCC TGCGGAGCC CCCCCACCC 3060
 CCAAGTCCC TCTCCGCC TTCACTGA AGAATGACT GGACTCTC GGGTGGGC 3120
 GGGAGAGCG CGACCCGAG GAGAGCAGT AGGAAGTAA GAGGCGAAA ACCCTCTTA 3180
 AGGAGAAGAA AAAAAAACA AAAAGTCTT CGAGAGTACT TCTAGAGCG CCGGGGCC 3240
 ATCGATTTTC CACCGGGTG GGGTACGAG TAAGTGACC CAATTGCCCT TATAGTGTG 3300
 CGATT

(2) INFORMATION FOR SEQ ID NO:11:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

TCCGGGGCCA GAGTGGGCTG

20

(2) INFORMATION FOR SEQ ID NO:12:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20 base pairs
- (B) TYPE: nucleic acid

(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

GCAGTCCTGG CCTGCGGATG

20

(2) INFORMATION FOR SEQ ID NO:13:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

GTGACAGGA GAATTGGTTC

20

(2) INFORMATION FOR SEQ ID NO:14:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

GCCTGGGTTT GGTGCGGGAC

20

(2) INFORMATION FOR SEQ ID NO:15:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

TGGTCGGGTG TTTGTGAGTG

20

(2) INFORMATION FOR SEQ ID NO:16:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

CCTCTCCGT CTCTCAGTG

20

(2) INFORMATION FOR SEQ ID NO:17:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

GGATTGCTAG TCTCACAGAC

20

(2) INFORMATION FOR SEQ ID NO:18:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

TTAAGGGTGG CTGAAGGGAC

20

(2) INFORMATION FOR SEQ ID NO:19:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

ACCTTCCTC CCTGTCACAG

20

(2) INFORMATION FOR SEQ ID NO:20:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:

TGGTCGGGTG TTTGTGAGTG

20

(2) INFORMATION FOR SEQ ID NO:21:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:

ACACCATCC AGAAATTCAG

20

(2) INFORMATION FOR SEQ ID NO:22:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:

AAACTGCAGG TGGCTGAGTC

20

(2) INFORMATION FOR SEQ ID NO:23:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:23: 20
 GTCCTAATGT TTTCAAGGAG

(2) INFORMATION FOR SEQ ID NO:24:

(i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 20 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:24: 20
 AAAACCTATG GTTCAATTG

(2) INFORMATION FOR SEQ ID NO:25:

(i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 20 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:25: 20
 TCCTAGACAT GGTCAAGT

(2) INFORMATION FOR SEQ ID NO:26:

(i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 20 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:26: 20
 GATATAATTA GTTCTCCATC

(2) INFORMATION FOR SEQ ID NO:27:

(i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 20 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:27: 20
 ATGCCTGTTC CAGGCTGCAC

(2) INFORMATION FOR SEQ ID NO:28:

(i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 20 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:28: 20
 GGACGGCGAC CTCCACCAC

(2) INFORMATION FOR SEQ ID NO:29:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:29:

GGGCTCCTCC GACGCTGAG 20

(2) INFORMATION FOR SEQ ID NO:30:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:30:

AGTCTAGCCC TGGCCTTGAC 20

(2) INFORMATION FOR SEQ ID NO:31:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:31:

GTCACGGGG ACTCCGGCAG 20

(2) INFORMATION FOR SEQ ID NO:32:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:32:

CAGCTTTCCC TGCGCACATG 20

(2) INFORMATION FOR SEQ ID NO:33:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:33:

CACAGCTGTC TCAAGCCCAG 20

(2) INFORMATION FOR SEQ ID NO:34:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:34:

ACTGTTCCCC CTACATGATG

20

(2) INFORMATION FOR SEQ ID NO:35:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:35:

ATCATATCCT CTTGCTGTC

20

(2) INFORMATION FOR SEQ ID NO:36:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:36:

GTTCACAGAG CTTGCTGTG

20

(2) INFORMATION FOR SEQ ID NO:37:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:37:

GTTTGGCAGA CTCATAGTTG

20

(2) INFORMATION FOR SEQ ID NO:38:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:38:

TAGCAGGGAG CCATGACCTG

20

(2) INFORMATION FOR SEQ ID NO:39:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:39:

CTTGGCGCCA GAAGCGAGAG

20

(2) INFORMATION FOR SEQ ID NO:40:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(x1) SEQUENCE DESCRIPTION: SEQ ID NO:40:

CCTCTCTCTC TCTCTCTC

20

(2) INFORMATION FOR SEQ ID NO:41:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(x1) SEQUENCE DESCRIPTION: SEQ ID NO:41:

TCCCCGCTGA TTCCGCCAAG

20

(2) INFORMATION FOR SEQ ID NO:42:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(x1) SEQUENCE DESCRIPTION: SEQ ID NO:42:

CTTTTGAAT TCGGCACGAG

20

(2) INFORMATION FOR SEQ ID NO:43:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(x1) SEQUENCE DESCRIPTION: SEQ ID NO:43:

CCCCTGGTCC GCACCAAGTT

20

(2) INFORMATION FOR SEQ ID NO:44:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(x1) SEQUENCE DESCRIPTION: SEQ ID NO:44:

GAGAAGGGTC GGGCGGCAG

20

(2) INFORMATION FOR SEQ ID NO:45:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(x1) SEQUENCE DESCRIPTION: SEQ ID NO:45:

AAATCACATC GCGTCAACAC

20

(2) INFORMATION FOR SEQ ID NO:46:

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:46:

TAAGAGAGTC ATAGTTACTC

20

(2) INFORMATION FOR SEQ ID NO:47:

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:47:

GCCTAGAGG TACTCTCGAG

20

(2) INFORMATION FOR SEQ ID NO:48:

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:48:

ACTCTGGCCA TCAGGAGATC

20

(2) INFORMATION FOR SEQ ID NO:49:

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:49:

CAGGCGTTGT AGATGTTCTG

20

(2) INFORMATION FOR SEQ ID NO:50:

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:50:

AGTGGCAGGC AGAAGTAATG

20

(2) INFORMATION FOR SEQ ID NO:51:

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:51:
GGTTGGAGAA CTGATGTAG 20

(2) INFORMATION FOR SEQ ID NO:52:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:52:
CTATTCAGAT GCAACGCCAG 20

(2) INFORMATION FOR SEQ ID NO:53:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:53:
CCATGGCACA CAGAGCAGAC 20

(2) INFORMATION FOR SEQ ID NO:54:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:54:
GCTACCATGC AGAGACACAG 20

(2) INFORMATION FOR SEQ ID NO:55:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:55:
CAGGCTGACA AGAAATCAG 20

(2) INFORMATION FOR SEQ ID NO:56:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:56:
GGCACGCATA GAGGAGAGAC 20

(2) INFORMATION FOR SEQ ID NO:57:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs

- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:57:

TGGGTGATGC CTTGCTGAC

20

(2) INFORMATION FOR SEQ ID NO:58:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 20 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:58:

AAAAACAAGT CAAGTGATG

20

(2) INFORMATION FOR SEQ ID NO:59:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 20 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:59:

TGCCCCACAT TGCTATGGT

20

(2) INFORMATION FOR SEQ ID NO:60:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 20 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:60:

GACCAAGATC AGAAGTAGAG

20

(2) INFORMATION FOR SEQ ID NO:61:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 20 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:61:

CCCTGGGCC AATGATGTTG

20

(2) INFORMATION FOR SEQ ID NO:62:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 19 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:62:

TCTCCACC ATAGCAATG

19

(2) INFORMATION FOR SEQ ID NO:63:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:63:

TGGTCTGGT GACCAATGTG

20

(2) INFORMATION FOR SEQ ID NO:64:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:64:

ACACCTCGGT GACCCCTGTG

20

(2) INFORMATION FOR SEQ ID NO:65:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:65:

TCTCCAAGTT CGGCACAGTG

20

(2) INFORMATION FOR SEQ ID NO:66:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:66:

ACATGGGCTG CACTCAGAC

20

(2) INFORMATION FOR SEQ ID NO:67:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:67:

GATCCTCTGA ACCTGCAGAG

20

(2) INFORMATION FOR SEQ ID NO:68:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:68:

GGAAATGAGG TGGGGCGATC

20

(2) INFORMATION FOR SEQ ID NO:69:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:69:

CTTTGCCTTG GACAAGGATG

20

(2) INFORMATION FOR SEQ ID NO:70:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:70:

GCACCTGCCA TTGGGGGTAG

20

(2) INFORMATION FOR SEQ ID NO:71:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:71:

GGTGGAGCC ATTGACGGTG

20

(2) INFORMATION FOR SEQ ID NO:72:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:72:

TGCGTCTCTC GTCGCTGCTG

20

(2) INFORMATION FOR SEQ ID NO:73:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:73:

GCGGAAACTC TGTGGTGCTG

20

(2) INFORMATION FOR SEQ ID NO:74:

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:74:

AGGATGGCCT TCCTCTACTG

20

(2) INFORMATION FOR SEQ ID NO:75:

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:75:

TGCTGTTC ACCAGGCAG

20

(2) INFORMATION FOR SEQ ID NO:76:

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:76:

CCAGTGCCTC TATGCATGTC

20

(2) INFORMATION FOR SEQ ID NO:77:

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:77:

AGGAAGCCCA CGCACACCAC

20

(2) INFORMATION FOR SEQ ID NO:78:

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:78:

CCGTTGTTC CCTGATCTTC

20

(2) INFORMATION FOR SEQ ID NO:79:

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:79:

CGCTCGGGAT CCAGTTCATC

20

(2) INFORMATION FOR SEQ ID NO:80:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:80:

TCGAGGTTCA GAGCGTAGTG

20

(2) INFORMATION FOR SEQ ID NO:81:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:81:

TCTTGGATCT CTGGCACCTC

20

(2) INFORMATION FOR SEQ ID NO:82:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:82:

CCATCAGAGT GAAGGAGGAG

20

(2) INFORMATION FOR SEQ ID NO:83:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:83:

CCATCTTCCA CTGGTCAGAG

20

(2) INFORMATION FOR SEQ ID NO:84:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:84:

CTCCTTCTCT TGGATCTCTG

20

(2) INFORMATION FOR SEQ ID NO:85:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20 base pairs
- (B) TYPE: nucleic acid

(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:85:

TTACTTCAGC ACTGTTAGTC

20

(2) INFORMATION FOR SEQ ID NO:86:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:86:

AGGGAGGTCG CTCAAAGCTC

20

(2) INFORMATION FOR SEQ ID NO:87:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:87:

TGGGTCCACA GTTCGACAG

20

(2) INFORMATION FOR SEQ ID NO:88:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:88:

CAACTCTGTG ATGGCTCCAG

20

(2) INFORMATION FOR SEQ ID NO:89:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:89:

AGCAGGGTTC TGTTCAAGAC

20

(2) INFORMATION FOR SEQ ID NO:90:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:90:

CCATTGGGTG CTAGTCTCTC

20

(2) INFORMATION FOR SEQ ID NO:91:

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:91:

CAGGCATGCT GTCCGAGCAG

20

(2) INFORMATION FOR SEQ ID NO:92:

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:92:

CTGACCTGA GGTAGCGCTG

20

(2) INFORMATION FOR SEQ ID NO:93:

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:93:

ATAACACCC TGAGGCACTG

20

(2) INFORMATION FOR SEQ ID NO:94:

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:94:

CCTGCAGTGC GACACTAGT

20

(2) INFORMATION FOR SEQ ID NO:95:

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:95:

AATTGGAATG AGGAGGACTG

20

(2) INFORMATION FOR SEQ ID NO:96:

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(x1) SEQUENCE DESCRIPTION: SEQ ID NO:96:
GCTCTAGAAG TACTCTCGAG 20

(2) INFORMATION FOR SEQ ID NO:97:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(x1) SEQUENCE DESCRIPTION: SEQ ID NO:97:
ATTGTATGAC AATGCACCAG 20

(2) INFORMATION FOR SEQ ID NO:98:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(x1) SEQUENCE DESCRIPTION: SEQ ID NO:98:
TCCACAGAGG GCTTCATCAC 20

(2) INFORMATION FOR SEQ ID NO:99:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(x1) SEQUENCE DESCRIPTION: SEQ ID NO:99:
CCTGACTGGC CTAAGCACAG 20

(2) INFORMATION FOR SEQ ID NO:100:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(x1) SEQUENCE DESCRIPTION: SEQ ID NO:100:
AAGCCTCATA ACCACCAAGT 20

(2) INFORMATION FOR SEQ ID NO:101:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(x1) SEQUENCE DESCRIPTION: SEQ ID NO:101:
TGTCACCGT GACAAGTG 20

(2) INFORMATION FOR SEQ ID NO:102:
(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:102:

TTGTACACCA GTCGAGGTC

20

(2) INFORMATION FOR SEQ ID NO:103:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:103:

GGGTGTGGTG CAGATGAGTC

20

(2) INFORMATION FOR SEQ ID NO:104:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:104:

ATCACACTCT TATAGCTCAG

20

(2) INFORMATION FOR SEQ ID NO:105:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:105:

GTGGGAAGCT TTCCTCAGAC

20

(2) INFORMATION FOR SEQ ID NO:106:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:106:

TGATGAACAT GGGCTGGAG

20

(2) INFORMATION FOR SEQ ID NO:107:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:107:

CATTGTGGAT GTACTACCAC

20

(2) INFORMATION FOR SEQ ID NO:108:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:108:

TGTGTTTTGC AACCTGAGTG

20

(2) INFORMATION FOR SEQ ID NO:109:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:109:

ATAGTGGCAC CACTTACGAG

20

(2) INFORMATION FOR SEQ ID NO:110:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:110:

AATTCTGCAA CGTGATGGCG

20

(2) INFORMATION FOR SEQ ID NO:111:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:111:

CACAAGATGC CTCGTCTGTG

20

(2) INFORMATION FOR SEQ ID NO:112:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:112:

AATCCGGACA AGGTACAGTC

20

(2) INFORMATION FOR SEQ ID NO:113:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:113:

GCACGAGTGG CACAAGCGTG

20

(2) INFORMATION FOR SEQ ID NO:114:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:114:

GCAAGCGTGT GGTGTCAGTG

20

(2) INFORMATION FOR SEQ ID NO:115:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:115:

TGTTTGAACA GGCTCTGGAC

20

(2) INFORMATION FOR SEQ ID NO:116:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:116:

CGGCATGGCA ATGAGGACAC

20

(2) INFORMATION FOR SEQ ID NO:117:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:117:

AGGACGAGAT GGACCTCCAG

20

(2) INFORMATION FOR SEQ ID NO:118:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:118:

CCCTCTGTCC TCTAGCCAC

20

(2) INFORMATION FOR SEQ ID NO:119:

(i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 20 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:119:

TCTTGAGGGG ACTGACTCTG 20

(2) INFORMATION FOR SEQ ID NO:120:

(i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 20 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:120:

TGAGTGAGGA GGCAGATGTC 20

(2) INFORMATION FOR SEQ ID NO:121:

(i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 20 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:121:

TGGCTTTGAA GAAAGAGCTG 20

(2) INFORMATION FOR SEQ ID NO:122:

(i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 20 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:122:

GC AAAAGACC AGGCTGACTG 20

(2) INFORMATION FOR SEQ ID NO:123:

(i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 20 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:123:

TGCAGCTCCT TGGTCTTCTC 20

(2) INFORMATION FOR SEQ ID NO:124:

(i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 20 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:124:
 GATTACAGT CCAAGGCTC 20

(2) INFORMATION FOR SEQ ID NO:125:

(i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 20 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:125:
 ATCTGATGA GCGGTTGAG 20

(2) INFORMATION FOR SEQ ID NO:126:

(i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 20 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:126:
 GTCACTCTC CGACGAGGAG 20

(2) INFORMATION FOR SEQ ID NO:127:

(i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 20 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:127:
 GGATCCAAAG TTCGTCTCTG 20

(2) INFORMATION FOR SEQ ID NO:128:

(i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 20 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:128:
 CGCTGTGTGT CTGATCCCTC 20

(2) INFORMATION FOR SEQ ID NO:129:

(i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 20 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:129:
 ATGAAGGTAA ACCCCGGGAG 20

(2) INFORMATION FOR SEQ ID NO:130:

(i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 20 base pairs

(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:130:

TGCTCTCTGG CTCTGAGCAC

20

(2) INFORMATION FOR SEQ ID NO:131:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:131:

GCCTGGAGAA GCCCAGTCTG

20

(2) INFORMATION FOR SEQ ID NO:132:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:132:

CACACTCTGG ACCGTTGCTG

20

(2) INFORMATION FOR SEQ ID NO:133:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:133:

AAAGCTCCGC AGCCGCAGTG

20

(2) INFORMATION FOR SEQ ID NO:134:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:134:

TCTCCAGGA AGCTGCGTGC

20

(2) INFORMATION FOR SEQ ID NO:135:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:135:

GATGTGTGGG CAGCATTGAG

20

(2) INFORMATION FOR SEQ ID NO:136:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:136:

GTCCACAGTG GTGCTGCAG

20

(2) INFORMATION FOR SEQ ID NO:137:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:137:

ACCTCACGGT TGCCAACCTG

20

(2) INFORMATION FOR SEQ ID NO:138:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:138:

CGCAACAGCG TCTCCCTCTG

20

(2) INFORMATION FOR SEQ ID NO:139:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:139:

AGTACCTTCA TAAGTTCTTC

20

(2) INFORMATION FOR SEQ ID NO:140:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:140:

TCCCAGACTT CAACCTTCAC

20

(2) INFORMATION FOR SEQ ID NO:141:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:141:

AAACATCTC CCGTCGGAC

20

(2) INFORMATION FOR SEQ ID NO:142:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:142:

GCTGAGCAC TTTACCTCAC

20

(2) INFORMATION FOR SEQ ID NO:143:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:143:

GACGTCGTC CGGAAGATG

20

(2) INFORMATION FOR SEQ ID NO:144:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:144:

ACACAGGAGA TGCAGGTAC

20

(2) INFORMATION FOR SEQ ID NO:145:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:145:

GAGTCTCCA TGAAGAACAG

20

(2) INFORMATION FOR SEQ ID NO:146:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:146:

GCAGTGAGGA AGGTAAAGAG

20

(2) INFORMATION FOR SEQ ID NO:147:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 4047 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: double
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Genomic DNA

(ix) FEATURE:

- (A) NAME/KEY: Coding Sequence
 (B) LOCATION: 378...1799
 (D) OTHER INFORMATION:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:147:

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GGATCCAAAG GACGCCCCCG CCGACAGGAG AATTGTTCC CGGCCCCGCG GCGATGCCCC 60
CCCGTAGCT CGGGCCCGTG GTCGGTGTT TGTAGTGT TCTATGTGGG AGAAGGAGGA 120
GGAGGAGGAA GAAGAAGCAA CGATTGTCT CTCGGCTGG TCTCCCCCGC GCTCTACATG 180
TTCCCCGCAC TGAGGAGACG GAAGAGGAGC CGTAGCGCC CCCCCTCCCG GCCCGGATTA 240
TAGTCTCTCG CCACACGGCG CTCGGCCTCC CTTTGATTG AGACGCCGAT TCGCCCAAGT 300
TTTGGGAAAT GGAAGATAAT GACAGCTGGC ACCTGAAC TAAGTCTTTA TAGGCAACAC 360
CATTTCCAGAA ATTCAGG ATG AAT GGG GAT ATG CCC CAT GTC CCC ATT ACT 410
Met Asn Gly Asp Met Pro His Val Pro Ile Thr
1 5 10

ACT CTT GCG GGG ATT GCT AGT CTC ACA GAC CTC CTG AAC CAG CTG CCT 458
Thr Leu Ala Gly Ile Ala Ser Leu Thr Asp Leu Leu Asn Gln Leu Pro
15 20 25

CTT CCA TCT CCT TTA CCT GCT ACA ACT ACA AAG AGC CTT CTC TTT AAT 506
Leu Pro Ser Pro Leu Pro Ala Thr Thr Lys Ser Leu Leu Phe Asn
30 35 40

GCA CGA ATA GCA GAA GAG GTG AAC TGC CTT TTG GCT TGT AGG GAT GAC 554
Ala Arg Ile Ala Glu Glu Val Asn Cys Leu Leu Ala Cys Arg Asp Asp
45 50 55

AAT TTG GTT TCA CAG CTT GTC CAT AGC CTC AAC CAG GTA TCA ACA GAT 602
Asn Leu Val Ser Gln Leu Val His Ser Leu Asn Gln Val Ser Thr Asp
60 65 70 75

CAC ATA GAG TTG AAA GAT AAC CTT GGC AGT GAT GAC CCA GAA GGT GAC 650
His Ile Glu Leu Lys Asp Asn Leu Gly Ser Asp Asp Pro Glu Gly Asp
80 85 90

ATA CCA GTC TTG TTG CAG GCC GTC CTG GCA AGG AGT CCT AAT GTT TTC 698
Ile Pro Val Leu Leu Gln Ala Val Leu Ala Arg Ser Pro Asn Val Phe
95 100 105

AGG GAG AAA AGC ATG CAG AAC AGA TAT GTA CAA AGT GGA ATG ATG ATG 746
Arg Glu Lys Ser Met Gln Asn Arg Tyr Val Gln Ser Gly Met Met Met
110 115 120

TCT CAG TAT AAA CTT TCT CAG AAT TCC ATG CAC AGT AGT CCT GCA TCT 794
Ser Gln Tyr Lys Leu Ser Gln Asn Ser Met His Ser Ser Pro Ala Ser
125 130 135

TCC AAT TAT CAA CAA ACC ACT ATC TCA CAT AGC CCC TCC AGC CGG TTT 842
Ser Asn Tyr Gln Gln Thr Thr Ile Ser His Ser Pro Ser Ser Arg Phe
140 145 150 155

GTG CCA CCA CAG ACA AGC TCT GGG AAC AGA TTT ATG CCA CAG CAA AAT 890
Val Pro Pro Gln Thr Ser Ser Gly Asn Arg Phe Met Pro Gln Gln Asn
160 165 170

AGC CCA GTG CCT AGT CCA TAC GCG CCA CAA AGC CCT GCA GGA TAC ATG 938
Ser Pro Val Pro Ser Pro Tyr Ala Pro Gln Ser Pro Ala Gly Tyr Met
175 180 185

CCA TAT TCC CAT CCT TCA AGT TAC ACA ACA CAT CCA CAG ATG CAA CAA 986
Pro Tyr Ser His Pro Ser Ser Tyr Thr Thr His Pro Gln Met Gln Gln
190 195 200

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GCA TCG GTA TCA AGT CCC ATT GTT GCA GGT GGT TTG AGA AAC ATA CAT 1034
 Ala Ser Val Ser Ser Pro Ile Val Ala Gly Gly Leu Arg Asn Ile His
 205 210 215
 GAT AAT AAA GTT TCT GGT CCG TTG TCT GGC AAT TCA GCT AAT CAT CAT 1082
 Asp Asn Lys Val Ser Gly Pro Leu Ser Gly Asn Ser Ala Asn His His
 220 225 230 235
 GCT GAT AAT CCT AGA CAT GGT TCA AGT GAG GAC TAC CTA CAC ATG GTG 1130
 Ala Asp Asn Pro Arg His Gly Ser Ser Glu Asp Tyr Leu His Met Val
 240 245 250
 CAC AGG CTA AGT AGT GAC GAT GGA GAT TCT TCA ACA ATG AGG AAT GCT 1178
 His Arg Leu Ser Ser Asp Asp Gly Asp Ser Ser Thr Met Arg Asn Ala
 255 260 265
 GCA TCT TTT CCC TTG AGA TCT CCA CAG CCA GTA TGC TCC CCT GCT GGA 1226
 Ala Ser Phe Pro Leu Arg Ser Pro Gln Pro Val Cys Ser Pro Ala Gly
 270 275 280
 AGT GAA GGA ACT CCT AAA GGC TCA AGA CCA CCT TTA ATC CTA CAA TCT 1274
 Ser Glu Gly Thr Pro Lys Gly Ser Arg Pro Pro Leu Ile Leu Gln Ser
 285 290 295
 CAG TCT CTA CTT TGT TCA TCA CCT CGA GAT GTT CCA CCA GAT ATC TTG 1322
 Gln Ser Leu Pro Cys Ser Ser Pro Arg Asp Val Pro Pro Asp Ile Leu
 300 305 310 315
 CTA GAT TCT CCA GAA AGA AAA CAA AAG AAG CAG AAG AAA ATG AAA TTA 1370
 Leu Asp Ser Pro Glu Arg Lys Gln Lys Lys Gln Lys Lys Met Lys Leu
 320 325 330
 GGC AAG GAT GAA AAA GAG CAG AGT GAG AAA GCG GCA ATG TAT GAT ATA 1418
 Gly Lys Asp Glu Lys Glu Lys Gln Ser Glu Lys Ala Ala Met Tyr Asp Ile
 335 340 345
 ATT AGT TCT CCA TCC AAG GAC TCT ACT AAA CTT ACA TTA AGA CTT TCT 1466
 Ile Ser Ser Pro Ser Lys Asp Ser Thr Lys Leu Thr Leu Arg Leu Ser
 350 355 360
 CGT GTA AGG TCT TCA GAC ATG GAC CAG CAA GAG GAT ATG ATT TCT GGT 1514
 Arg Val Arg Ser Ser Asp Met Asp Gln Gln Glu Asp Met Ile Ser Gly
 365 370 375
 GTG GAA AAT AGC AAT GTT TCA GAA AAT GAT ATT CCT TTT AAT GTG CAG 1562
 Val Glu Asn Ser Asn Val Ser Glu Asn Asp Ile Pro Phe Asn Val Gln
 380 385 390 395
 TAC CCA GGA CAG ACT TCA AAA ACA CCC ATT ACT CCA CAA GAT ATA AAC 1610
 Tyr Pro Gly Gln Thr Ser Lys Thr Pro Ile Thr Pro Gln Asp Ile Asn
 400 405 410
 CGC CCA CTA AAT GCT GCT CAA TGT TTG TCG CAG CAA GAA CAA ACA GCA 1658
 Arg Pro Leu Asn Ala Ala Gln Cys Leu Ser Gln Gln Glu Gln Thr Ala
 415 420 425
 TTC CTT CCA GCA AAT CAA GTG CCT GTT TTA CAA CAG AAC ACT CTA GTT 1706
 Phe Leu Pro Ala Asn Gln Val Pro Val Leu Gln Gln Asn Thr Ser Val
 430 435 440
 GCT GCA AAA CAA CCC CAG ACC AAT AGT CAC AAA ACC TTG GTG CAG CCT 1754
 Ala Ala Lys Gln Pro Gln Thr Asn Ser His Lys Thr Leu Val Gln Pro
 445 450 455
 GGA ACA GGC ATA GAG GTC TCA GCA GAG CTG CCC AAG GAC AAG ACC TAAGA 1804
 Gly Thr Gly Ile Glu Val Ser Ala Glu Leu Pro Lys Asp Lys Thr
 460 465 470
 TCCAGCAGGG AACTATGTAG TCACCCGAG AGGCCAGCT CTCTCCGTGA GCTCTGGGCC 1864
 TAGGGTGGGG GTGGTGTGTG GTTCTGCGCG CACTGTTCCT CCTACATGAT GGGTCCATCC 1924
 CAGTGTGGCT CTCTCACTCG GTTCTCTCTG TGGAGAGGCC TGTCAGGTG TCACCTGCTC 1984
 CAGGAGACGT CTCTGATTTC CTCCAGTTGA ACAGTGAGAT TTGCACACC TCACATGAT 2044
 CGCTTCTGTC CTGGAATTG TAACATAGG TTTTCTGTG TCCTGGAGGA CAAGGATGAG 2104

GGCTTCCAC TTGAGTCTCC CTGGTGGAGC CCAGCTCCTG ACATACCTGG TAAAGTTCT 2164
 CAAGAGAAGA ACATGGGAGG GGAATGTGGA TAACAACCTT GGCCTGCTGT GTGTTCCAAG 2224
 CTAGGAAGAT GTAATGTGCG CAGAACGGGG GTAAATGGCT TGCTGCGCTC ACAGCTGTCT 2284
 CAAGCCAGG CCTGSGGGC CAGCCCAAGC CCAAGSACTA GGTCCAGAGC CACACGCGC 2344
 CAGGCACAT CGGCTCACC TGGGACCCCT TGTGGGTCAT AGTCTCCGGC CCACCCAGA 2404
 CTTCTGAAG GAGAGACCC ATGGCAAGGA CTCAGCCACC TGCAGTTCA TAAGCCCCCA 2464
 GTGGGTCTCT AGGCATGAAG ACCACCGGTT AGAGGCTGAA CTGGCAGGAA CTTGTCTCCA 2524
 GCGCCTTCTC ACCCCAGCGC GGGCCTGCCT CAGAGCGAGC ACCCAGGAGC TGCCCATGAC 2584
 CCGTGACTC CACTCAATCC CTCTTCTCCA GGAGCCATGC AAAGTGTAGC CCAGCCAGGC 2644
 CCGTGGAAGG CAGTCATCAC CTCTTAAGG ATTGTGGGTG TCGGTCTCTG AACTGCCAGG 2704
 TGGAGCACAC GAGCCGTGTC CGGTGTTCGA TAGCAGGGA GATCAGCTTG GCACCATTC 2764
 CACGCTCAA GGGGACCCCG GGGGGCCCTG GGTGGGGGCG GATCAGCTTT CCCTGEGGAC 2824
 ATCTGCTCTA TTGACAGTCT CAGAGGCTCA TGTCTGTAG AGGGAGGGA GGTCTGCCCC 2884
 TGCGCTTCCG TCACTCTTCC CAGTCAGGCT TGCGCAGCCT GGGCTTTAGA GCTGGCTTCT 2944
 GCGCCACACT TCTCGGTGA AGGAAACAA CTATGAGTCT GCCAAACGCA TCTCAGATGC 3004
 GGTTTAAAAA ATTTCTGGTCC CGGCTCTCTG TCCCATCATC CGCCTCGGGC ACTTCTCTCT 3064
 TCGGTGGTCT TCACCCCAT A CTCTGTCACT GCCACATTT CACCTGGGCG TGCCCTTTGT 3124
 CTCACACTGA AACTCTGAA AATCTTGAA TGGATTCTA GGTCACTGGG GACTCCGGCA 3184
 GCACATTCGG CTTCAGAATA AAGGGCGCGC CGGCTCCCC AGCACCCTCC CAAGCACAC 3244
 CCCATGCTC CTCTCCATC CTCTGAGCCT GAGGTCTCCT TCAGCCACCC TTAASTCCCC 3304
 ACCTGGGCTC CTGGCCCGCC CTGGGTAGC AGCGCTTCT CACCGGGGCG CATGACCTG AAAGCTAGC 3364
 CACAGAGGCC CCTCACTCT CTGGGATGA GGGGCGAGG GGTGGGCTG CCGCTCTGCT 3424
 CTTGGCTTGC ACCTCCGAG AGCCGCTCC CGGCTCTCT CCGGCCCCGG CCGGCTCTCT 3484
 TGCTGCTGGC CTCTGGGTG TGCCCGCGAG ACTGAGCTGC GCTTGGGGGT CCGTGGGCGC 3544
 TGGGCGCTCC CGCACGGAAC CAGGCGGCTG GGAGCCCGCG GGGAGGGGCG GAGGTCTCTC 3604
 TGGGGGCTCC TCCAGGCTCT GAGGGGCTGT CTTCCCCGCG GCGCGCCGCG GTTCTCGG 3664
 AGCCGGGGCC TCCGCTCTCG GGTGACCCGG TGAGACCCCG GGGGAGGGCG CTGGGGAGGC 3724
 GCGGGCTCTG CTCCCGGGT CCAAAAGCAC TGGCTGCCCC TCAGGAGGGA CGGGCAGCTC 3784
 CACCCACGGC GCTGGCGCCC GACAGCGCGC TCTCTCCGCT CCGGAGCCT GGAGCGCTCC 3844
 CAGAGCGGCC CCGCGGSGCC CACAGCGGCG CCGCATCCG AGGCAGAGC TGGCTTCCG 3904
 GAGCTGGGCG CCGCCAGCCT GAGAGGAGCG GCGCCAGAG CCGTCCAGC CTTCCACAG 3964
 CCACCTGGC CCGCGAGGCC CGGCTGCTC CAGTGGGCG TCTCTGGGCC CGGCTTTCC 4024
 CGGGGAAGA AAGCAAAAAG CTT

(2) INFORMATION FOR SEQ ID NO:148:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 474 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

- (ii) MOLECULE TYPE: protein
 (v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:148:

Met Asn Gly Asp Met Pro His Val Pro Ile Thr Thr Leu Ala Gly Ile
 1 10 15
 Ala Ser Leu Thr Asp Leu Leu Asn Gln Leu Pro Leu Pro Ser Pro Leu
 20 25 30
 Pro Ala Thr Thr Thr Lys Ser Leu Leu Phe Asn Ala Arg Ile Ala Glu
 35 40 45
 Glu Val Asn Cys Leu Leu Ala Cys Arg Asp Asp Asn Leu Val Ser Gln
 50 55 60
 Leu Val His Ser Leu Asn Gln Val Ser Thr Asp His Ile Glu Leu Lys
 65 70 75 80
 Asp Asn Leu Gly Ser Asp Asp Pro Glu Gly Asp Ile Pro Val Leu Leu
 85 90 95
 Gln Ala Val Leu Ala Arg Ser Pro Asn Val Phe Arg Glu Lys Ser Met
 100 105 110
 Gln Asn Arg Tyr Val Gln Ser Gly Met Met Ser Gln Tyr Lys Leu
 115 120 125
 Ser Gln Asn Ser Met His Ser Ser Pro Ala Ser Ser Asn Tyr Gln Gln
 130 135 140
 Thr Thr Ile Ser His Ser Pro Ser Arg Phe Val Pro Pro Gln Thr
 145 150 155 160
 Ser Ser Gly Asn Arg Phe Met Pro Gln Gln Asn Ser Pro Val Pro Ser
 165 170 175
 Pro Tyr Ala Pro Gln Ser Pro Ala Gly Tyr Met Pro Tyr Ser His Pro
 180 185 190
 Ser Ser Tyr Thr Thr His Pro Gln Met Gln Gln Ala Ser Val Ser Ser
 195 200 205

[illegible]

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 2998 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(A) NAME/KEY: Coding Sequence
(B) LOCATION: 26...799
(C) OTHER INFORMATION:

AAGCTTTTGTG AATTCGGCAC GAGAT	GCT ACA CAG GCT ATA TTT GAA ATA CTG	52
	Ala Thr Gln Ala Ile Phe Glu Ile Leu	
	1 5	
GAG AAA TCC TGG TTG CCC CAG AAT TGT ATA CTG GTT GAT ATG AAG ATT	Glu Lys Ser Trp Leu Pro Gln Asn Cys Thr Leu Val Asp Met Lys Ile	100
10 15 20 25		
GAA TTT GGT GTT GAT GTA ACC ACC AAA GAA ATT GTT CTT GCT GAT GTT	Glu Phe Gly Val Asp Val Thr Thr Lys Glu Ile Val Gct Ala Asp Val	148
30 35 40		
ATT GAC AAT GAT TCC TGG AGA CTC TGG CCA TCA GGA GAT CGA AGC CAA	Ile Asp Asn Asp Ser Pro Arg Leu Thr Pro Ser Gly Asp Arg Ser Gln	196
45 50 55		
CAG AAA GAC AAA CAG TCT TAT CGG GAG CTC GAA GAA GTA ACT CCT GAA	Gln Lys Asp Lys Gln Ser Tyr Arg Asp Asp Leu Lys Glu Val Thr Pro Glu	244
60 65 70		
GGG CTC CAA ATG GTA AAG AAA AAC TTT GAG TGG GTT GCA GAG AGA GTA		292

Gly Leu Gln Met Val Lys Lys Asn Phe Glu Trp Val Ala Glu Arg Val
75 80 85

GAG TTG CTT TTG AAA TCA GAA AGT CAG TGC AGG GTT GTA GTG TTG ATG 340
Glu Leu Leu Leu Lys Ser Glu Ser Gln Cys Arg Val Val Val Leu Met
90 95 100 105

GGC TCT ACT TCT GAT CTT GGT CAC TGT GAA AAA ATC AAG GCC TGT 388
Gly Ser Thr Ser Asp Leu Gly His Cys Glu Lys Ile Lys Lys Ala Cys
110 115 120

GGA AAT TTT GGC ATT CCA TGT GAA CTT CGA GTA ACA TCT GCG CAT AAA 436
Gly Asn Phe Gly Ile Pro Cys Glu Leu Arg Val Thr Ser Ala His Lys
125 130 135

GGA CCA GAT GAA ACT CTG AGG ATT AAA GCT GAG TAT GAA GGG GAT GGC 484
Gly Pro Asp Glu Thr Leu Arg Ile Lys Ala Glu Tyr Glu Gly Asp Gly
140 145 150

ATT CCT ACT GTA TTT GTG GCA GTG GCA GGC AGA AGT AAT GGT TTG GGA 532
Ile Pro Thr Val Phe Val Ala Val Ala Gly Arg Ser Asn Gly Leu Gly
155 160 165

CCA GTG ATG TCT GGG AAC ACT GCA TAT CCA GTT ATC AGC TGT CCT CCC 580
Pro Val Met Ser Gly Asn Thr Ala Tyr Pro Val Ile Ser Cys Pro Pro
170 175 180 185

CTC ACA CCA GAC TGG GGA GTT CAG GAT GTG TGG TCT TCT CTT CGA CTA 628
Leu Thr Pro Asp Trp Gly Val Gln Asp Val Trp Ser Ser Leu Arg Leu
190 195 200

CCC AGT GGT CTT GGC TGT TCA ACC GTA CTT TCT CCA GAA GGA TCA GCT 676
Pro Ser Gly Leu Gly Cys Ser Thr Val Leu Ser Pro Glu Gly Ser Ala
205 210 215

CAA TTT GCT GCT CAG ATA TTT GGG TTA AGC AAC CAT TTG GTA TGG AGC 724
Gln Phe Ala Ala Gln Ile Phe Gly Leu Ser Asn His Leu Val Trp Ser
220 225 230

AAA CTG CGA GCA AGC ATT TTG AAC ACA TGG ATT TCC TTG AAG CAG GCT 772
Lys Leu Arg Ala Ser Ile Leu Asn Thr Trp Ile Ser Leu Lys Gln Ala
235 240 245

GAC AAG AAA ATC AGA GAA TGT AAT TTA TAAGAAAGAA TGCCATTGAA TTTTITA 826
Asp Lys Lys Ile Arg Glu Cys Asn Leu
250 255

GGGAAAAAC TACAAATTTT TAATTAGCT GAAGGAAAT CAAGCAAGAT GAAAAGGTAA 886
TTTTAAATTA GAGAACACAA ATAAATGT TAAGTAATA AATGGTGAAG GTAGGCCATT 944
TCAGATTGCAA GGCCAGCAAT GGGGCTCCCC ATATTCCCCA CCCCCTTGTT CCGAGTCCCC 1006
TTCTCTGCAA TGGGCACGCA TAGAGGAGAG ACAAGGGTA TTAGACGCAA CATCATTTGC 1066
CCAGGGGAGT CCGAAGAGAG GTCCCATTTG CTGACAGGCC ATTTTCAGGC TCTGTCATTG 1126
GTACGGGAGC ACACCCCAAG CTGAAGAGTG ATGCCATTGG CCAGGGAGTG GTTTTGTGCT 1186
AGCCGTTGGC TGTGAAGTGG AAGGAAAGA TCTGGGAATG AAGCCCTGTG GCCAGGAAGA 1246,
TAGACAGGGC AGCAACTTCT GGGCCTCCAG GGCCTCTTCC CACCATAGCA ATGTGGGCAA 1306
AAGTGGTGTG AGGCCCCAGC CAGAAAAAGG AGCCCAAGCC AGAGGGCAG TGACAAAGA 1366
TGATCATGCT CCAATCTCCC ACACCTGGG GCTGCCCTTC CCAATGCTTT TCTGTATAGC 1426
CAAGTTGGGC TGGGAGCAGC TCACTGCTCC TTAGGCCAAG AGGGTTTCTC AGCTCCGGA 1486
GGCCGAGCT TGATGTTGAA CTGCTGAGG GTCTGCTCCA GCTGTTCTG GTTCCGACGA 1546
AAGTAGGGGG ACACAGCAT GTTGAAGAGC AGCAGCTGCT TGTCGATCAT CTTGATCTTG 1606
TTTTCTTCCA GGAACCTGAG CTTGATGGCC ACATCTCCCC GCAAGCTCTC ATACTGTGTC 1666
CGATGGGCTT GGAAGTGGC CTGGGCACTC TCAAGTCGAG CAGCTGTCCC TGCAATCCGG 1726
GGGCCATAGC TCAGCTCCTC TAAGTCTGTT CGGTAGGCAT CATATTCCAG CCTGGCAGCC 1786
TCATAGTGTG TCACAGTCAT GAGCGTGTCT TCCATGGTCT TGGTGACCAA TGTGTTGATG 1846
CTAGAGACAA AGAAGTTTAC GGCTCCTAGC AGCGTTTCCC CATCTTGCCA TAGATGTTTC 1906
TGTGTTCTG CATTTGAGC AATATCTCC TGAAGCTCTG GGAAGTCTG GCTGAAGTCA 1966
GCAAGGCAAT CACCCAGTGC ATGCTGGGTC TGACAGAGGC GTTAGAGTG GCGTGTGAGT 2026
GCCCGCCCCA GCTGCAGGAC ACTCTCATAC TTGCGCTTGG TCTCAGCAG CAACCTCAATC 2086
TTCAGCTCTA GCTCCAGGAT TCCGGGCGCT CCACTCGCTC CCCCAGGGGT CTGCTCTGTG 2146
TGCCATGGAC GGCATTGTCC CAGATATAGC CGTTGGTACA AAGCGGGGAT CTGACGAGCT 2206
TTTCTCTACT TGTGTCACTA ACGGACCGTT TATCATGAGC AGCACTCGCC CTTCGACAGC 2266
AAACGGAAAT GACAGCAAGA AGTTCAAAGG TGACAGCCGA AGTGCAGGCG TCCCCTCTAG 2326
AGTGATCCAC ATCCGGAAGC TCCCATCGA CGTCAGGAG GGGGAAGTCA TCTCCCTGGG 2386

GCTGCCCTTT GGGAGGTCA CCAACCTCT GATGCTGAAG GGGAAAAACC AGGCCCTTCAT 2446
 CGAGATGAAC ACGGAGGAGG CTGCCAATAC CATGGTGAAC TACTACACCT CGGTGACCCC 2506
 TGTGCTGCGC GGGCAGGCCA TCTACATCCA GTTCTCCAAC CACAAGGAGC TGAAGACCGA 2566
 CAGCTCTCCC AACGAGGCC GGGCCAGGC GGCCTGGAG CGGTGAACCT CGGTCCAGTC 2626
 GGGGAACCTG GCCTTGGCTG CCTCGCGGC GGCCTGGAT GCAGGATGG CGATGGCGGG 2686
 GCAGAGCCCC GTGCTCAGGA TCATCGTGGG GAACCTCTTC TACCCTGTGA CCCTGGATGT 2746
 GCTGCACCAAG ATTTTCTCCA AGTTCGGCAC AGTGTGAAG ATCATCACCT TCACCAAGAA 2806
 CAACCAAGTTC CAGGCCCTGC TGCAGTATGC GAGCCCCGTG AGGCCCCAGC AGCCCAAGCT 2866
 GTGCTGGAGC GGGCAGAAC TCTACAACGC CTGCTGCAGC CTGGCATTGC ACTTTTCCAA 2926
 GCTCACCAGC CTCAACGTCA AGTACAACAA TGACAAGAGC CGTGACTACC TCGTGCCGAA 2986
 TTCTTGGAT CC 2998

(2) INFORMATION FOR SEQ ID NO:150:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 258 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:150:

Ala Thr Gln Ala Ile Phe Glu Ile Leu Glu Lys Ser Trp Leu Pro Gln
 1 5 10 15
 Asn Cys Thr Leu Val Asp Met Lys Ile Glu Phe Gly Val Asp Val Thr
 20 25 30
 Thr Lys Glu Ile Val Leu Ala Asp Val Ile Asp Asn Asp Ser Trp Arg
 35 40 45
 Leu Trp Pro Ser Gly Asp Arg Ser Gln Gln Lys Asp Lys Gln Ser Tyr
 50 55 60
 Arg Asp Leu Lys Glu Val Thr Pro Glu Gly Leu Gln Met Val Lys Lys
 65 70 75 80
 Asn Phe Glu Trp Val Ala Glu Arg Val Glu Leu Leu Lys Ser Glu
 85 90 95
 Ser Gln Cys Arg Val Val Val Leu Met Gly Ser Thr Ser Asp Leu Gly
 100 105 110
 His Cys Glu Lys Ile Lys Lys Ala Cys Gly Asn Phe Gly Ile Pro Cys
 115 120 125
 Glu Leu Arg Val Thr Ser Ala His Lys Gly Pro Asp Glu Thr Leu Arg
 130 135 140
 Ile Lys Ala Glu Tyr Glu Gly Asp Gly Ile Pro Thr Val Phe Val Ala
 145 150 155 160
 Val Ala Gly Arg Ser Asn Gly Leu Gly Pro Val Met Ser Gly Asn Thr
 165 170 175
 Ala Tyr Pro Val Ile Ser Cys Pro Pro Leu Thr Pro Asp Trp Gly Val
 180 185 190
 Gln Asp Val Trp Ser Ser Leu Arg Leu Pro Ser Gly Leu Gly Cys Ser
 195 200 205
 Thr Val Leu Ser Pro Glu Gly Ser Ala Gln Phe Ala Ala Gln Ile Phe
 210 215 220
 Gly Leu Ser Asn His Leu Val Trp Ser Lys Leu Arg Ala Ser Ile Leu
 225 230 235 240
 Asn Thr Trp Ile Ser Leu Lys Gln Ala Asp Lys Lys Ile Arg Glu Cys
 245 250 255
 Asn Leu

(2) INFORMATION FOR SEQ ID NO:151:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1038 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:151:

Ile Gln Arg Phe Gly Thr Ser Gly His Ile Met Asn Leu Gln Ala Gln
 1 5 10 15

Pro Lys Ala Gln Asn Lys Arg Lys Arg Cys Leu Phe Gly Gly Gln Glu
 20 25 30
 Pro Ala Pro Lys Glu Gln Pro Pro Leu Gln Pro Pro Gln Gln Ser
 35 40 45
 Ile Arg Val Lys Glu Glu Gln Tyr Leu Gly His Glu Gly Pro Gly Gly
 50 55 60
 Ala Val Ser Thr Ser Gln Pro Val Glu Leu Pro Pro Ser Ser Leu
 65 70 75 80
 Ala Leu Leu Asn Ser Val Val Tyr Gly Pro Glu Arg Thr Ser Ala Ala
 85 90 95
 Met Leu Ser Gln Gln Val Ala Ser Val Lys Trp Pro Asn Ser Val Met
 100 105 110
 Ala Pro Gly Arg Gly Pro Glu Arg Gly Gly Gly Gly Val Ser Asp
 115 120 125
 Ser Ser Trp Gln Gln Gln Pro Gly Gln Pro Pro His Ser Thr Trp
 130 135 140
 Asn Cys His Ser Leu Ser Leu Tyr Ser Ala Thr Lys Gly Ser Pro His
 145 150 155 160
 Pro Gly Val Gly Val Pro Thr Tyr Tyr Asn His Pro Glu Ala Leu Lys
 165 170 175
 Arg Glu Lys Ala Gly Gly Pro Gln Leu Asp Arg Tyr Val Arg Pro Met
 180 185 190
 Met Pro Gln Lys Val Gln Leu Glu Val Gly Arg Pro Gln Ala Pro Leu
 195 200 205
 Asn Ser Phe His Ala Ala Lys Lys Pro Pro Asn Gln Ser Leu Pro Leu
 210 215 220
 Gln Pro Phe Gln Leu Ala Phe Gly His Gln Val Asn Arg Gln Val Phe
 225 230 235 240
 Arg Gln Gly Pro Pro Pro Asn Pro Val Ala Ala Phe Pro Pro Gln
 245 250 255
 Lys Gln Gln Gln Gln Gln Pro Gln Gln Gln Gln Gln Gln
 260 265 270
 Ala Ala Leu Pro Gln Met Pro Leu Phe Glu Asn Phe Tyr Ser Met Pro
 275 280 285
 Gln Gln Pro Ser Gln Gln Pro Gln Asp Phe Gly Leu Gln Pro Ala Gly
 290 295 300
 Pro Leu Gly Gln Ser His Leu Ala His His Ser Met Ala Pro Tyr Pro
 305 310 315 320
 Phe Pro Pro Asn Pro Asp Met Asn Pro Glu Leu Arg Lys Ala Leu Leu
 325 330 335
 Gln Asp Ser Ala Pro Gln Pro Ala Leu Pro Gln Val Gln Ile Pro Phe
 340 345 350
 Pro Arg Arg Ser Arg Arg Leu Ser Lys Glu Gly Ile Leu Pro Pro Ser
 355 360 365
 Ala Leu Asp Gly Ala Gly Thr Gln Pro Gly Gln Glu Ala Thr Gly Asn
 370 375 380
 Leu Phe Leu His His Trp Pro Leu Gln Gln Pro Pro Gly Ser Leu
 385 390 395 400
 Gly Gln Pro His Pro Glu Ala Leu Gly Phe Pro Leu Glu Leu Arg Glu
 405 410 415
 Ser Gln Leu Leu Pro Asp Gly Glu Arg Leu Ala Pro Asn Gly Arg Glu
 420 425 430
 Arg Glu Ala Pro Ala Met Gly Ser Glu Glu Gly Met Arg Ala Val Ser
 435 440 445
 Thr Gly Asp Cys Gly Gln Val Leu Arg Gly Gly Val Ile Gln Ser Thr
 450 455 460
 Arg Arg Arg Arg Ala Ser Gln Glu Ala Asn Leu Leu Thr Leu Ala
 465 470 475 480
 Gln Lys Ala Val Glu Leu Ala Ser Leu Gln Asn Ala Lys Asp Gly Ser
 485 490 495
 Gly Ser Glu Glu Lys Arg Lys Ser Val Leu Ala Ser Thr Thr Lys Cys
 500 505 510
 Gly Val Glu Phe Ser Glu Pro Ser Leu Ala Thr Lys Arg Ala Arg Glu
 515 520 525
 Asp Ser Gly Met Val Pro Leu Ile Ile Pro Val Ser Val Pro Val Arg
 530 535 540
 Thr Val Asp Pro Thr Glu Ala Ala Gln Ala Gly Gly Leu Asp Glu Asp
 545 550 555 560
 Gly Lys Gly Leu Glu Gln Asn Pro Ala Glu His Lys Pro Ser Val Ile
 565 570 575
 Val Thr Arg Arg Arg Ser Thr Arg Ile Pro Gly Thr Asp Ala Gln Ala
 580 585 590
 Gln Ala Glu Asp Met Asn Val Lys Leu Glu Gly Glu Pro Ser Val Arg

595 600 605
 Lys Pro Lys Gln Arg Pro Arg Pro Glu Pro Leu Ile Ile Pro Thr Lys
 610 615 620
 Ala Gly Thr Phe Ile Ala Pro Pro Val Tyr Ser Asn Ile Thr Pro Tyr
 625 630 635 640
 Gln Ser His Leu Arg Ser Pro Val Arg Leu Ala Asp His Pro Ser Glu
 645 650 655
 Arg Ser Phe Glu Leu Pro Pro Tyr Thr Pro Pro Pro Ile Leu Ser Pro
 660 665 670
 Val Arg Glu Gly Ser Gly Leu Tyr Phe Asn Ala Ile Ile Ser Thr Ser
 675 680 685
 Thr Ile Pro Ala Pro Pro Pro Ile Thr Pro Lys Ser Ala His Arg Thr
 690 695 700
 Leu Leu Arg Thr Asn Ser Ala Glu Val Thr Pro Pro Val Leu Ser Val
 705 710 715 720
 Met Gly Glu Ala Thr Pro Val Ser Ile Glu Pro Arg Ile Asn Val Gly
 725 730 735
 Ser Arg Phe Gln Ala Glu Ile Pro Leu Met Arg Asp Arg Ala Leu Ala
 740 745 750
 Ala Ala Asp Pro His Lys Ala Asp Leu Val Trp Gln Pro Trp Glu Asp
 755 760 765
 Leu Glu Ser Ser Arg Glu Lys Gln Arg Gln Val Glu Asp Leu Leu Thr
 770 775 780
 Ala Ala Cys Ser Ser Ile Phe Pro Gly Ala Gly Thr Asn Gln Glu Leu
 785 790 795 800
 Ala Leu His Cys Leu His Glu Ser Arg Gly Asp Ile Leu Glu Thr Leu
 805 810 815
 Asn Lys Leu Leu Leu Lys Lys Pro Leu Arg Pro His Asn His Pro Leu
 820 825 830
 Ala Thr Tyr His Tyr Thr Gly Ser Asp Gln Trp Lys Met Ala Glu Arg
 835 840 845
 Lys Leu Phe Asn Lys Gly Ile Ala Ile Tyr Lys Lys Asp Phe Phe Leu
 850 855 860
 Val Gln Lys Leu Ile Gln Thr Lys Thr Val Ala Gln Cys Val Glu Phe
 865 870 875 880
 Tyr Tyr Thr Tyr Lys Lys Gln Val Lys Ile Gly Arg Asn Gly Thr Leu
 885 890 895
 Thr Phe Gly Asp Val Asp Thr Ser Asp Glu Lys Ser Ala Gln Glu Glu
 900 905 910
 Val Glu Val Asp Ile Lys Thr Ser Gln Lys Phe Pro Arg Val Pro Leu
 915 920 925
 Pro Arg Arg Glu Ser Pro Ser Glu Glu Arg Leu Glu Pro Lys Arg Glu
 930 935 940
 Val Lys Glu Pro Arg Lys Glu Gly Glu Glu Val Pro Glu Ile Gln
 945 950 955 960
 Glu Lys Glu Glu Gln Glu Glu Gly Arg Glu Arg Ser Arg Arg Ala Ala
 965 970 975
 Ala Val Lys Ala Thr Gln Thr Leu Gln Ala Asn Glu Ser Ala Ser Asp
 980 985 990
 Ile Leu Ile Leu Arg Ser His Glu Ser Asn Ala Pro Gly Ser Ala Gly
 995 1000 1005
 Gly Gln Ala Ser Glu Lys Pro Arg Glu Gly Thr Gly Lys Ser Arg Arg
 1010 1015 1020
 Ala Leu Pro Phe Ser Glu Lys Lys Lys Lys Gln Lys Ala
 1025 1030 1035

(2) INFORMATION FOR SEQ ID NO:152:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 849 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:152:

Ile Arg His Glu Val Ser Phe Leu Trp Asn Thr Glu Ala Ala Cys Pro
 1 5 10 15
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 20 25 30
 Asn Ser Gly Phe Val Phe Asn Leu Asn Pro Leu Asn Ser Ser Gln Gly
 35 40 45

Tyr Asn Val Ser Gly Ile Gly Lys Ile Phe Met Phe Asn Val Cys Gly
 50 55 60
 Thr Met Pro Val Cys Gly Thr Ile Leu Gly Lys Pro Ala Ser Gly Cys
 65 70 75 80
 Glu Ala Glu Thr Gln Thr Glu Glu Leu Lys Asn Trp Lys Pro Ala Arg
 85 90 95
 Pro Val Gly Ile Glu Lys Ser Leu Gln Leu Ser Thr Glu Gly Phe Ile
 100 105 110
 Thr Leu Thr Tyr Lys Gly Pro Leu Ser Ala Lys Gly Thr Ala Asp Ala
 115 120 125
 Phe Ile Val Arg Phe Val Cys Asn Asp Asp Val Tyr Ser Gly Pro Leu
 130 135 140
 Lys Phe Leu His Gln Asp Ile Asp Ser Gly Gln Gly Ile Arg Asn Thr
 145 150 155 160
 Tyr Phe Glu Phe Glu Thr Ala Leu Ala Cys Val Pro Ser Pro Val Asp
 165 170 175
 Cys Gln Val Thr Asp Leu Ala Gly Asn Glu Tyr Asp Leu Thr Gly Leu
 180 185 190
 Ser Thr Val Arg Lys Pro Trp Thr Ala Val Asp Thr Ser Val Asp Gly
 195 200 205
 Arg Lys Arg Thr Phe Tyr Leu Ser Val Cys Asn Pro Leu Pro Tyr Ile
 210 215 220
 Pro Gly Cys Gln Gly Ser Ala Val Gly Ser Cys Leu Val Ser Glu Gly
 225 230 235 240
 Asn Ser Trp Asn Leu Gly Val Val Gln Met Ser Pro Gln Ala Ala Ala
 245 250 255
 Asn Gly Ser Leu Ser Ile Met Tyr Val Asn Gly Asp Lys Cys Gly Asn
 260 265 270
 Gln Arg Phe Ser Thr Arg Ile Thr Phe Glu Cys Ala Gln Ile Ser Gly
 275 280 285
 Ser Pro Ala Phe Gln Leu Gln Asp Gly Cys Glu Tyr Val Phe Ile Trp
 290 295 300
 Arg Thr Val Glu Ala Cys Pro Val Val Arg Val Glu Gly Asp Asn Cys
 305 310 315 320
 Glu Val Lys Asp Pro Arg His Gly Asn Leu Tyr Asp Leu Lys Pro Leu
 325 330 335
 Gly Leu Asn Asp Thr Ile Val Ser Ala Gly Glu Tyr Thr Tyr Phe
 340 345 350
 Arg Val Cys Gly Lys Leu Ser Ser Asp Val Cys Pro Thr Ser Asp Lys
 355 360 365
 Ser Lys Val Val Ser Ser Cys Gln Glu Lys Arg Glu Pro Gln Gly Phe
 370 375 380
 His Lys Val Ala Gly Leu Leu Thr Gln Lys Leu Thr Tyr Glu Asn Gly
 385 390 395 400
 Leu Leu Lys Met Asn Phe Thr Gly Gly Asp Thr Cys His Lys Val Tyr
 405 410 415
 Gln Arg Ser Thr Ala Ile Phe Phe Tyr Cys Asp Arg Gly Thr Gln Arg
 420 425 430
 Pro Val Phe Leu Lys Glu Thr Ser Asp Cys Ser Tyr Leu Phe Glu Trp
 435 440 445
 Arg Thr Gln Tyr Ala Cys Pro Pro Phe Asp Leu Thr Glu Cys Ser Phe
 450 455 460
 Lys Asp Gly Ala Gly Asn Ser Phe Asp Leu Ser Ser Leu Ser Arg Tyr
 465 470 475 480
 Ser Asp Asn Trp Glu Ala Ile Thr Gly Thr Gly Asp Pro Glu His Tyr
 485 490 495
 Leu Ile Asn Val Cys Lys Ser Leu Ala Pro Gln Ala Gly Thr Glu Pro
 500 505 510
 Cys Pro Pro Glu Ala Ala Ala Cys Leu Leu Gly Gly Ser Lys Pro Val
 515 520 525
 Asn Leu Gly Arg Val Arg Asp Gly Pro Gln Trp Arg Asp Gly Ile Ile
 530 535 540
 Val Leu Lys Tyr Val Asp Gly Asp Leu Cys Pro Asp Gly Ile Arg Lys
 545 550 555 560
 Lys Ser Thr Thr Ile Arg Phe Thr Cys Ser Glu Ser Gln Val Asn Ser
 565 570 575
 Arg Pro Met Phe Ile Ser Ala Val Glu Asp Cys Glu Tyr Thr Phe Ala
 580 585 590
 Trp Pro Thr Ala Thr Ala Cys Pro Met Lys Ser Asn Glu His Asp Asp
 595 600 605
 Cys Gln Val Thr Asn Pro Ser Thr Gly His Leu Phe Asp Leu Ser Ser
 610 615 620
 Leu Ser Gly Arg Ala Gly Phe Thr Ala Ala Tyr Ser Glu Lys Gly Leu

625 630 635 640
 Val Tyr Met Ser Ile Cys Gly Glu Asn Glu Asn Cys Pro Pro Gly Val
 645 650 655
 Gly Ala Cys Phe Gly Gln Thr Arg Ile Ser Val Gly Lys Ala Asn Lys
 660 665 670
 Arg Leu Arg Tyr Val Asp Gln Val Leu Gln Leu Val Tyr Lys Asp Gly
 675 680 685
 Ser Pro Cys Pro Ser Lys Ser Gly Leu Ser Tyr Lys Ser Val Ile Ser
 690 695 700
 Phe Val Cys Arg Pro Glu Ala Gly Pro Thr Asn Arg Pro Met Leu Ile
 705 710 715 720
 Ser Leu Asp Lys Gln Thr Cys Thr Leu Phe Phe Ser Trp His Thr Pro
 725 730 735
 Leu Ala Cys Glu Gln Ala Thr Glu Cys Ser Val Arg Asn Gly Ser Ser
 740 745 750
 Ile Val Asp Leu Ser Pro Leu Ile His Arg Thr Gly Gly Tyr Glu Ala
 755 760 765
 Tyr Asp Glu Ser Glu Asp Asp Ala Ser Asp Thr Asn Pro Asp Phe Tyr
 770 775 780
 Ile Asn Ile Cys Gln Pro Leu Asn Pro Met His Gly Val Pro Cys Pro
 785 790 795 800
 Ala Gly Ala Ala Val Cys Lys Val Pro Ile Asp Gly Pro Pro Ile Asp
 805 810 815
 Ile Gly Arg Val Ala Gly Pro Pro Ile Leu Asn Pro Ile Ala Asn Glu
 820 825 830
 Ile Tyr Leu Asn Phe Glu Ser Ser Thr Pro Cys Gln Glu Phe Ser Cys
 835 840 845
 Lys

(2) INFORMATION FOR SEQ ID NO:153:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 852 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:153:

Met Ala Arg Leu Ser Arg Pro Glu Arg Pro Asp Leu Val Phe Glu Glu
 1 5 10 15
 Glu Asp Leu Pro Tyr Glu Glu Glu Ile Met Arg Asn Gln Phe Ser Val
 20 25 30
 Lys Cys Trp Leu His Tyr Ile Glu Phe Lys Gln Gly Ala Pro Lys Pro
 35 40 45
 Arg Leu Asn Gln Leu Tyr Tyr Glu Arg Ala Leu Lys Leu Leu Pro Cys Ser
 50 55 60
 Tyr Lys Leu Trp Tyr Arg Tyr Leu Lys Ala Arg Arg Ala Gln Val Lys
 65 70 75 80
 His Arg Cys Val Thr Asp Pro Ala Tyr Glu Asp Val Asn Asn Cys His
 85 90 95
 Glu Arg Ala Phe Val Phe Met His Lys Met Pro Arg Leu Trp Leu Asp
 100 105 110
 Tyr Cys Gln Phe Leu Met Asp Gln Gly Arg Val Thr His Thr Arg Arg
 115 120 125
 Thr Phe Asp Arg Ala Leu Arg Ala Leu Pro Ile Thr Gln His Ser Arg
 130 135 140
 Ile Trp Pro Leu Tyr Leu Arg Phe Leu Arg Ser His Pro Leu Pro Glu
 145 150 155 160
 Thr Ala Val Arg Gly Tyr Arg Arg Phe Leu Lys Leu Ser Pro Glu Ser
 165 170 175
 Ala Glu Glu Tyr Ile Glu Tyr Leu Lys Ser Ser Asp Arg Leu Asp Glu
 180 185 190
 Ala Ala Gln Arg Leu Ala Thr Val Val Asn Asp Glu Arg Phe Val Ser
 195 200 205
 Lys Ala Gly Lys Ser Asn Tyr Gln Leu Trp His Glu Leu Cys Asp Leu
 210 215 220
 Ile Ser Gln Asn Pro Asp Lys Val Gln Ser Leu Asn Val Asp Ala Ile
 225 230 235 240
 Ile Arg Gly Leu Thr Arg Phe Thr Asp Gln Leu Gly Lys Leu Trp
 245 250 255

Cys Ser Leu Ala Asp Tyr Tyr Ile Arg Ser Gly His Phe Glu Lys Ala
 260 265 270
 Arg Asp Val Tyr Glu Glu Ala Ile Arg Thr Val Met Thr Val Arg Asp
 275 280 285
 Phe Thr Gln Val Phe Asp Ser Tyr Ala Gln Phe Glu Glu Ser Met Ile
 290 295 300
 Ala Ala Lys Met Glu Thr Ala Ser Glu Leu Gly Arg Glu Glu Glu Asp
 305 310 315 320
 Asp Val Asp Leu Glu Leu Arg Leu Ala Arg Phe Glu Gln Leu Ile Ser
 325 330 335
 Arg Arg Pro Leu Leu Leu Asn Ser Val Leu Leu Arg Gln Asn Pro His
 340 345 350
 His Val His Glu Trp His Lys Arg Val Ala Leu His Gln Gly Arg Pro
 355 360 365
 Arg Glu Ile Ile Asn Thr Tyr Thr Glu Ala Val Gln Thr Val Asp Pro
 370 375 380
 Phe Lys Ala Thr Gly Lys Pro His Thr Leu Trp Val Ala Phe Ala Lys
 385 390 395 400
 Phe Tyr Glu Asp Asn Gly Gln Leu Asp Asp Ala Arg Val Ile Leu Glu
 405 410 415
 Lys Ala Thr Lys Val Asn Phe Lys Gln Val Asp Asp Leu Ala Ser Val
 420 425 430
 Trp Cys Gln Cys Gly Glu Leu Glu Leu Arg His Glu Asn Tyr Asp Glu
 435 440 445
 Ala Leu Arg Leu Leu Arg Lys Ala Thr Ala Leu Pro Ala Arg Arg Ala
 450 455 460
 Glu Tyr Phe Asp Gly Ser Glu Pro Val Gln Asn Arg Val Tyr Lys Ser
 465 470 475 480
 Leu Lys Val Trp Ser Met Leu Ala Asp Leu Glu Glu Ser Leu Gly Thr
 485 490 495
 Phe Gln Ser Thr Lys Ala Val Tyr Asp Arg Ile Leu Asp Leu Arg Ile
 500 505 510
 Ala Thr Pro Gln Ile Val Ile Asn Tyr Ala Met Phe Leu Glu Glu His
 515 520 525
 Lys Tyr Phe Glu Glu Ser Phe Lys Ala Tyr Glu Arg Gly Ile Ser Leu
 530 535 540
 Phe Lys Trp Pro Asn Val Ser Asp Ile Trp Ser Thr Tyr Leu Thr Lys
 545 550 555 560
 Phe Ile Ala Arg Tyr Gly Gly Arg Lys Leu Glu Arg Ala Arg Asp Leu
 565 570 575
 Phe Glu Gln Ala Leu Asp Gly Cys Pro Pro Lys Tyr Ala Lys Thr Leu
 580 585 590
 Tyr Leu Leu Tyr Ala Gln Leu Glu Glu Glu Trp Gly Leu Ala Arg His
 595 600 605
 Ala Met Ala Val Tyr Glu Arg Ala Thr Arg Ala Val Glu Pro Ala Gln
 610 615 620
 Gln Tyr Asp Met Phe Asn Ile Tyr Ile Lys Arg Ala Ala Glu Ile Tyr
 625 630 635 640
 Gly Val Thr His Thr Arg Gly Ile Tyr Gln Lys Ala Ile Glu Val Leu
 645 650 655
 Ser Asp Glu His Ala Arg Glu Met Cys Leu Arg Phe Ala Asp Met Glu
 660 665 670
 Cys Lys Leu Gly Glu Ile Asp Arg Ala Arg Ala Ile Tyr Ser Phe Cys
 675 680 685
 Ser Gln Ile Cys Asp Pro Arg Thr Thr Gly Ala Phe Trp Gln Thr Trp
 690 695 700
 Lys Asp Phe Glu Val Arg His Gly Asn Glu Asp Thr Ile Lys Glu Met
 705 710 715 720
 Leu Arg Ile Arg Arg Ser Val Gln Ala Thr Tyr Asn Thr Gln Val Asn
 725 730 735
 Phe Met Ala Ser Gln Met Leu Lys Val Ser Gly Ser Ala Thr Gly Thr
 740 745 750
 Val Ser Asp Leu Ala Pro Gly Gln Ser Gly Met Asp Asp Met Lys Leu
 755 760 765
 Leu Glu Gln Arg Ala Glu Gln Leu Ala Ala Glu Ala Glu Arg Asp Gln
 770 775 780
 Pro Leu Arg Ala Gln Ser Lys Ile Leu Phe Val Arg Ser Asp Ala Ser
 785 790 795 800
 Arg Glu Glu Leu Ala Glu Leu Ala Gln Gln Val Asn Pro Glu Glu Ile
 805 810 815
 Gln Leu Gly Glu Asp Glu Asp Glu Asp Glu Met Asp Leu Glu Pro Asn
 820 825 830
 Glu Val Arg Leu Glu Gln Gln Ser Val Pro Ala Ala Val Phe Gly Ser

835
Leu Lys Glu Asp
850

840

845

(2) INFORMATION FOR SEQ ID NO:154:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 693 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:154:

```

Met Phe Ser Ala Leu Lys Lys Leu Val Gly Ser Asp Gln Ala Pro Gly
 1           5           10           15
Arg Asp Lys Asn Ile Pro Ala Gly Leu Gln Ser Met Asn Gln Ala Leu
 20           25           30
Gln Arg Arg Phe Ala Lys Gly Val Gln Tyr Asn Met Lys Ile Val Ile
 35           40           45
Arg Gly Asp Arg Asn Thr Gly Lys Thr Ala Leu Trp His Arg Leu Gln
 50           55           60
Gly Arg Pro Phe Val Glu Glu Tyr Ile Pro Thr Gln Glu Ile Gln Val
 65           70           75           80
Thr Ser Ile His Trp Ser Tyr Lys Thr Thr Asp Asp Ile Val Lys Val
 85           90           95
Glu Val Trp Asp Val Val Asp Lys Gly Lys Cys Lys Lys Arg Gly Asp
100           105           110
Gly Leu Lys Met Glu Asn Asp Pro Gln Glu Xaa Glu Ser Glu Met Ala
115           120           125
Leu Asp Ala Glu Phe Leu Asp Val Tyr Lys Asn Cys Asn Gly Val Val
130           135           140
Met Met Phe Asp Ile Thr Lys Gln Trp Thr Phe Asn Tyr Ile Leu Arg
145           150           155           160
Glu Leu Pro Lys Val Pro Thr His Val Pro Val Cys Val Leu Gly Asn
165           170           175
Tyr Arg Asp Met Gly Glu His Arg Val Ile Leu Pro Asp Asp Val Arg
180           185           190
Asp Phe Ile Asp Asn Leu Asp Arg Pro Pro Gly Ser Ser Tyr Phe Arg
195           200           205
Tyr Ala Glu Ser Ser Met Lys Asn Ser Phe Gly Leu Lys Tyr Leu His
210           215           220
Lys Phe Phe Asn Ile Pro Phe Leu Gln Leu Gln Arg Glu Thr Leu Leu
225           230           235           240
Arg Gln Leu Glu Thr Asn Gln Leu Asp Met Asp Ala Thr Leu Glu Glu
245           250           255
Leu Ser Val Gln Gln Glu Thr Glu Asp Gln Asn Tyr Gly Ile Phe Leu
260           265           270
Glu Met Met Glu Ala Arg Ser Arg Gly His Ala Ser Pro Leu Ala Ala
275           280           285
Asn Gly Gln Ser Pro Ser Pro Gly Ser Gln Ser Pro Val Leu Pro Ala
290           295           300
Pro Ala Val Ser Thr Gly Ser Ser Ser Pro Gly Thr Pro Gln Pro Ala
305           310           315           320
Pro Gln Leu Pro Leu Asn Ala Ala Pro Pro Ser Ser Val Pro Pro Val
325           330           335
Pro Pro Ser Glu Ala Leu Pro Pro Pro Ala Cys Pro Ser Ala Pro Ala
340           345           350
Pro Arg Arg Ser Ile Ile Ser Arg Leu Phe Gly Thr Ser Pro Ala Thr
355           360           365
Glu Ala Ala Pro Pro Pro Pro Glu Pro Val Pro Ala Ala Gln Gly Pro
370           375           380
Ala Thr Val Gln Ser Val Glu Asp Phe Val Pro Asp Asp Arg Leu Asp
385           390           395           400
Arg Ser Phe Leu Glu Asp Thr Thr Pro Ala Arg Asp Glu Lys Lys Val
405           410           415
Gly Ala Lys Ala Ala Gln Gln Asp Ser Asp Ser Asp Gly Glu Ala Leu
420           425           430
Gly Gly Asn Pro Met Val Ala Gly Phe Gln Asp Asp Val Asp Leu Glu
435           440           445           450
Asp Gln Pro Arg Gly Ser Pro Pro Leu Pro Ala Gly Pro Val Pro Ser
455           460

```

Gln Asp Ile Thr Leu Ser Ser Glu Glu Glu Ala Glu Val Ala Ala Pro 480
 465 470 475
 Thr Lys Gly Pro Ala Pro Ala Pro Gln Gln Cys Ser Glu Pro Glu Thr 495
 485 490
 Lys Trp Ser Ser Ile Pro Ala Ser Lys Pro Arg Gly Thr Ala Pro 510
 500 505
 Thr Arg Thr Ala Ala Pro Pro Trp Pro Gly Gly Val Ser Val Arg Thr 525
 515 520
 Gly Pro Glu Lys Arg Ser Ser Thr Arg Pro Pro Ala Glu Met Glu Pro 540
 530 535
 Gly Lys Gly Glu Gln Ala Ser Ser Ser Glu Ser Asp Pro Glu Gly Pro 560
 545 550 555
 Ile Ala Ala Gln Met Leu Ser Phe Val Met Asp Pro Asp Phe Glu 575
 565 570
 Ser Glu Gly Ser Asp Thr Gln Arg Arg Ala Asp Asp Phe Pro Val Arg 590
 580 585
 Asp Asp Pro Ser Asp Val Thr Asp Glu Asp Glu Gly Pro Ala Glu Pro 605
 595 600
 Pro Pro Pro Pro Lys Leu Pro Leu Pro Ala Phe Arg Leu Lys Asn Asp 620
 610 615
 Ser Asp Leu Phe Gly Leu Gly Leu Glu Ala Gly Pro Lys Glu Ser 640
 625 630 635
 Ser Glu Glu Gly Lys Glu Gly Lys Thr Pro Ser Lys Glu Lys Lys 655
 645 650
 Lys Thr Lys Ser Phe Ser Arg Val Leu Leu Glu Arg Pro Arg Ala His 670
 660 665
 Arg Phe Ser Thr Arg Val Gly Tyr Gln Val Ser Val Pro Asn Ser Pro 685
 675 680
 Tyr Ser Glu Ser Tyr 690

CLAIMS

What is claimed as the invention is:

1. An isolated polynucleotide comprising a nucleotide sequence with the following properties:
 - a) the sequence is expressed at the mRNA level in Jurkat T cells;
 - b) when COS-1 cells expressing TNF receptor are genetically altered to express the sequence, the cells have increased enzymatic activity for cleaving and releasing the receptor.
2. The polynucleotide of claim 1, wherein the nucleotide sequence is contained in a sequence selected from the group consisting of
 - a) SEQ. ID NO:1;
 - b) SEQ. ID NO:2 or SEQ. ID NO:3;
 - c) SEQ. ID NO:4;
 - d) SEQ. ID NO:5;
 - e) SEQ. ID NO:6;
 - f) SEQ. ID NO:7;
 - g) SEQ. ID NO:8;
 - h) SEQ. ID NO:9; and
 - i) SEQ. ID NO:10.
3. An isolated polynucleotide comprising at least 30 consecutive nucleotides in said nucleotide sequence of a polynucleotide according to any of claims 1-3
4. An isolated polynucleotide comprising a linear sequence of at least 50 consecutive nucleotides at least 90% identical to a sequence contained in said nucleotide sequence of the polynucleotide of claim 1.

5. An isolated polynucleotide of at least 50 nucleotides capable of hybridizing specifically to said nucleotide sequence of a polynucleotide according to any of claims 1-3 at 68°C in 0.5 M phosphate buffer pH 7, 7% SDS, and 100 µg/mL salmon sperm DNA, followed by washing in a buffer containing 3X SSC.
6. An antisense polynucleotide or ribozyme comprising at least 10 consecutive nucleotides in said nucleotide sequence of a polynucleotide according to claim 1 or 2, which inhibits the expression of a TRRE modulator.
7. An isolated polypeptide comprising an amino acid sequence encoded by a polynucleotide according to any of claims 1-5.
8. The polypeptide of claim 7, selected from the group consisting of SEQ. ID NOS: 147-158.
9. An isolated polypeptide, comprising at least 10 consecutive residues in said amino acid sequence of a polypeptide according to claim 7 or 8.
10. An isolated polypeptide, comprising at least 15 consecutive amino acids which are at least 80% identical to a sequence contained in said amino acid sequence of the polypeptide according to claim 7 or 8.
11. The polypeptide of claim 7-11, which when incubated with COS-1 cells expressing TNF receptor, promotes enzymatic cleavage and release of the receptor.
12. The polypeptide of claims 7-11, which either:
- a) lacks a membrane spanning sequence; or

b) is produced by a process comprising recombinant expression in a host cell followed by purification of the polypeptide from medium in which the cell is cultured.

13. A method of producing the polypeptide according to any of claims 7 to 11, comprising the steps of:

- a) culturing host cells genetically altered to express the polynucleotide according to claim 3; and subsequently
- b) purifying the polypeptide from the cells.

14. The method according to claim 13, comprising harvesting culture medium following step a); and purifying the polypeptide from the culture medium by a process comprising affinity chromatography.

15. An isolated polynucleotide encoding the polypeptide of claim 8 or 9.

16. An isolated antibody specific for a polypeptide according any of claims 7-11.

17. A method for producing the antibody according to claim 16, comprising immunizing a mammal or contacting an immunocompetent cell or particle with a polypeptide according to claim 9 or 10.

18. An assay method of determining altered TRRE activity in a cell or tissue sample, comprising the steps of:

- a) contacting the sample with the polynucleotide of claim 4 or 5 under conditions that permit the polynucleotide to hybridize specifically with nucleic acid that encodes a modulator of TRRE activity, if present in the sample; and
- b) determining polynucleotide that has hybridized as a result of step a), as a measure of altered TRRE activity in the sample.

19. An assay method for determining altered expression of a modulator of TRRE activity in a cell or tissue sample, comprising the steps of:
- a) contacting the sample with the antibody of claim 16 under conditions that permit the antibody to bind the modulator if present in the sample, thereby forming an antibody-antigen complex; and
 - b) determining complex formed in step a), as a measure of the modulator.
20. A method for assessing a disease condition associated with altered TRRE activity in a subject, comprising determining altered TRRE activity in the sample from the subject according to claim 18, or determining altered expression of a TRRE modulator according to claim 19, and then correlating the extent of alteration with the disease condition.
21. A method for decreasing signal transduction from a cytokine into a cell, comprising contacting the cell with a polypeptide according to any of claims 7-8 and 11-12, or with a polynucleotide according to any of claims 1-3 and 15.
22. A method for increasing signal transduction from a cytokine into a cell, comprising contacting the cell with a polynucleotide according to claim 6, or with an antibody according to claim 16.
23. The method according to claim 21 or claim 22, wherein the cytokine is TNF.
24. A method for screening polynucleotides for an ability to modulate TRRE activity, comprising the steps of:
- a) providing cells that express both TRRE and the TNF-receptor;
 - b) genetically altering the cells with the polynucleotides to be screened;
 - c) cloning the cells genetically altered in step b); and

d) identifying clones that enzymatically release the receptor at an altered rate.

25. A method for screening substances for an ability to affect TRRE activity, comprising the steps of:

- a) incubating cells expressing TNF receptor with a polypeptide according to claim 9 in the presence of the substance;
- b) incubating cells expressing TNF receptor with a polypeptide according to claim 9 in the absence of the substance;
- c) measuring any TNF receptor released from the cells in steps a) and b); and
- d) correlating an increase or decrease of the receptor released in step a) relative to that in step b) with an ability of the substance to enhance or diminish TRRE activity.

26. Use of a polypeptide according to any of claims 7-8 or 11-12, in the preparation of a medicament for treatment of the human or animal body by surgery or therapy.

27. Use of a polynucleotide according to any of claims 1-3, 6, or 15 in the preparation of a medicament for treatment of the human or animal body by surgery or therapy.

28. Use of an antibody according to claim 16, in the preparation of a medicament for treatment of the human or animal body by surgery or therapy.

29. Use of a polypeptide according to any of claims 7-8 and 11-12, a polynucleotide according to any of claims 1-3 and 15 or an antibody according to claim 16, in the preparation of a medicament for treatment of a

disease selected from the group consisting of heart failure, cachexia, inflammation, endotoxic shock, arthritis, multiple sclerosis, and sepsis.

30. A method of treating cancer in a subject, comprising increasing signal transduction from TNF into cells at the site of the cancer in the subject according to claim 22 or 23.

31. A method of treating a disease selected from the group consisting of heart failure, cachexia, inflammation, endotoxic shock, arthritis, multiple sclerosis, and sepsis, comprising decreasing signal transduction from TNF into cells at the site of the disease in the subject according to claim 21 or 23.

32. The method of claim 31, comprising administering to the subject an effective amount of the polypeptide of any of claims 7-8 or 11-12.

ABSTRACT OF THE DISCLOSURE

The biological effects of the cytokine TNF are mediated by binding to receptors on the surface of cells. This disclosure describes new proteins and polynucleotides that promote enzymatic cleavage and release of TNF receptors. Also provided are methods for identifying additional compounds that influence TNF receptor shedding. As the active ingredient in a pharmaceutical composition, the products of this invention increase or decrease TNF signal transduction, thereby alleviating the pathology of disease.

10

Figure 1

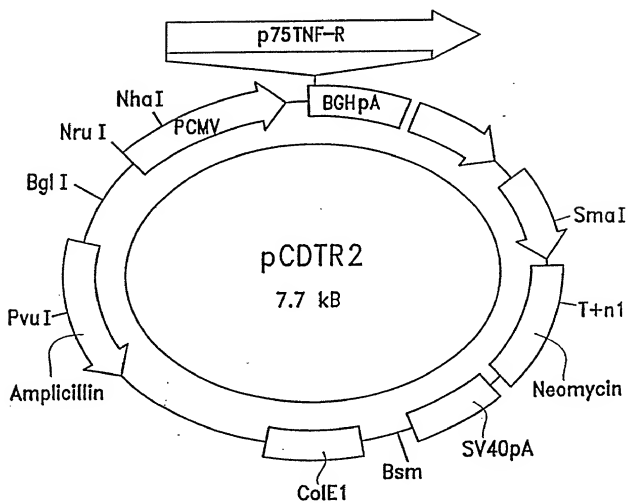


Figure 2

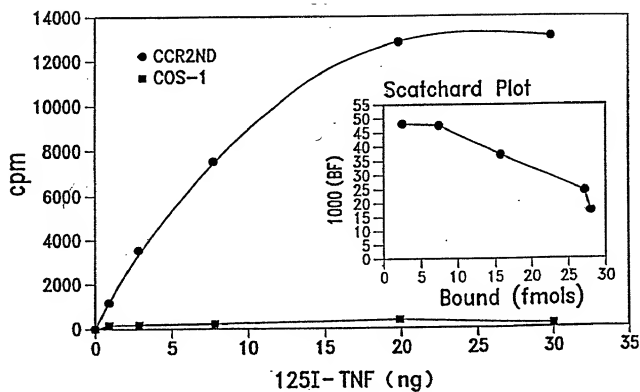


Figure 3

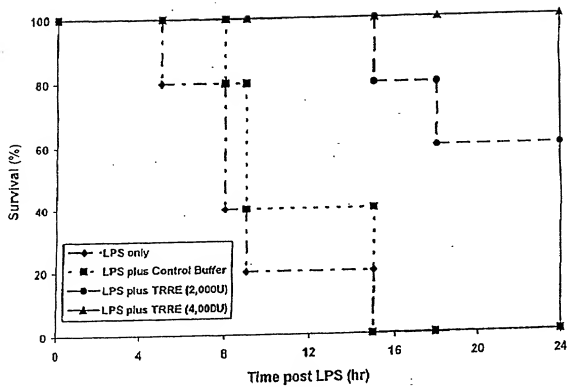


Figure 4

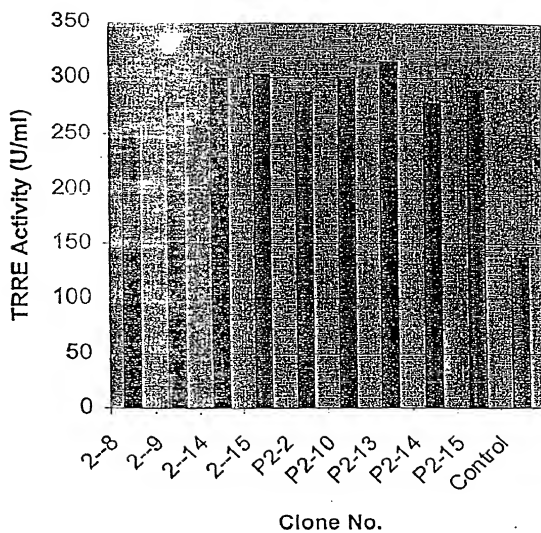
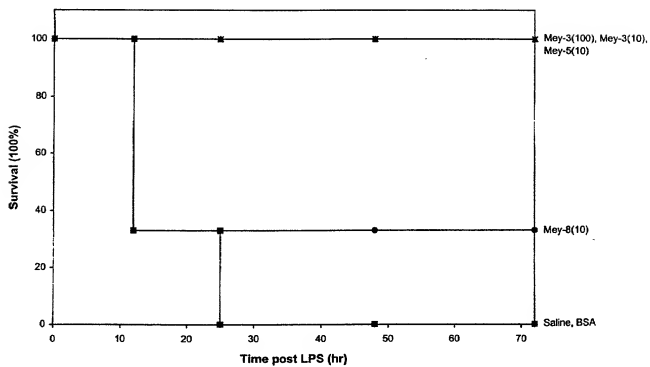


Figure 5

**Treatment of Mey proteins to prevent from mortality induced by LPS plus
D-Galactosamine**



**DECLARATION FOR UTILITY OR
DESIGN PATENT APPLICATION
(37 CFR 1.63)**

☒ Declaration Submitted with Initial Filing OR ☐ Declaration Submitted after Initial Filing (surcharge (37 CFR 1.16(e)) required)

Attorney Docket Number	IRVN-007CON
First Named Inventor	Gatanaga, et al.
COMPLETE IF KNOWN	
Application Number	N/A
Filing Date	Herewith
Group Art Unit	N/A
Examiner Name	N/A

As a below named inventor, I hereby declare that:

My residence, post office address, and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

Factors Affecting Tumor Necrosis Factor Receptor Releasing Enzyme Activity

the specification of which:

☒ is attached hereto

OR

☐ was filed on _____ as United States Application Number or PCT International Application Number _____ and was amended on _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment specifically referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined by 37 CFR 1.56.

Insofar as the subject matter of each of the claims of this application are not disclosed in the prior United States or PCT international application in the manner provided by the first paragraph of 35 U.S.C. 412, I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application.

I hereby claim foreign priority benefits under 35 U.S.C. 119(a)-(d) or 365(b) of any foreign application(s) for patent or inventor's certificate, or 365(a) of any PCT international application which designating at least one country other than the United States of America, listed below and have also identified below any foreign application(s) for patent or inventor's certificate or any PCT international application(s) having a filing date before that of the application(s) of which priority is claimed.

Prior Foreign Application Number(s)	Country	Foreign Filing Date (MM/DD/YYYY)	Priority Not Claimed	Certified Copy Attached?	
				YES	NO
	PCT		<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>

I hereby claim the benefit under 35 U.S.C. 119(e) of any United States provisional application(s) listed below.

Application Number(s)	Filing Date (MM/DD/YYYY)

I hereby claim the benefit under 35 U.S.C. 120 of any United States application(s), or 365(c) of any PCT international application(s) designating the United States of America, listed below.

U.S. Parent Application or PCT Parent Number	Parent Filing Date (MM/DD/YYYY)	Parent Patent Number (if applicable)
09/081,385	05/14/1998	
PCT/US99/10793	05/14/1999	

NOV-13-00 MON 09:17 AM BOZICEVIC FIELD&FRANCIS , FAX NO. 650 327+3231

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Atty Dkt No. IRVN-007CON

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Country	U.S.A.	Telephone	650-327-3400	Facsimile	650-327-3231

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Name of Sole or First Inventor:

Given Name (first and middle (if any))				Family Name or Surname			
Tetsuya				Galanaga			
Inventor's Signature						Date	
Residence: City	Irvine	State	CA	Country	USA	Citizenship	JAPAN
Post Office Address	77 Wellesley						
City	Irvine	State	CA	Zip	92612	Country	USA

Name of Second Inventor:

Given Name (first and middle (if any))				Family Name or Surname			
Gale A.				Granger			
Inventor's Signature	<i>Gale A. Granger</i>					Date	13 NOV 00
Residence: City	Laguna Beach	State	CA	Country	USA	Citizenship	USA
Post Office Address	31562 Santa Rosa						
City	Laguna Beach	State	CA	Zip	92651	Country	USA

**DECLARATION FOR UTILITY OR
DESIGN PATENT APPLICATION
(37 CFR 1.63)**

☒ Declaration Submitted with Initial Filing or ☐ Declaration Submitted after Initial Filing (surcharge (37 CFR 1.16(e)) required)

Attorney Docket Number	IRVN-007CON
First Named Inventor	Gatanaga, et al.
COMPLETE IF KNOWN	
Application Number	N/A
Filing Date	Herewith
Group Art Unit	N/A
Examiner Name	N/A

As a below named inventor, I hereby declare that:

My residence, post office address, and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

Factors Affecting Tumor Necrosis Factor Receptor Releasing Enzyme Activity

the specification of which:

☒ is attached hereto

OR

☐ was filed on _____ as United States Application Number or PCT International Application Number _____ and was amended on _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment specifically referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined by 37 CFR 1.56.

Insofar as the subject matter of each of the claims of this application are not disclosed in the prior United States or PCT international application in the manner provided by the first paragraph of 35 U.S.C. 112, I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application.

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Prior Foreign Application Number(s)	Country	Foreign Filing Date (MM/DD/YYYY)	Priority Not Claimed	Certified Copy Attached?	
				YES	NO
	PCT		<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>

I hereby claim the benefit under 35 U.S.C. 119(e) of any United States provisional application(s) listed below.

Application Number(s)	Filing Date (MM/DD/YYYY)

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U.S. Parent Application or PCT Parent Number	Parent Filing Date (MM/DD/YYYY)	Parent Patent Number (if applicable)
09/081,385	05/14/1998	
PCT/US99/10793	05/14/1999	

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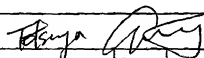
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Atty Dkt No. IRVN-007CON

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Name of Sole or First Inventor:

Given Name (first and middle [if any])				Family Name or Surname			
Tetsuya				Gatanaga			
Inventor's Signature						Date	11/13/00
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Name of Second Inventor:

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Galo A.				Granger			
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Post Office Address	31562 Santa Rosa						
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